

# **Unlicensed ‘special’ medicines; improving the patients’ experience**

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# Summary

Unlicensed 'special' medicines are used frequently around the world. Often used to treat children, the elderly and those with complex or rare clinical conditions, unlicensed 'special' medicines have not been through clinical trials and are not manufactured in commercial quantities like licensed medicines. As a result of this, unlicensed 'special' medicines may be harder to access after discharge (Wong *et al*, 2006). The aim of the thesis was to explore the views and experiences of those involved in prescribing, obtaining, supplying and receiving unlicensed 'special' medicines in Wales, in the hopes of being able to provide evidence-based recommendations for change.

A systematic review was conducted to identify factors within the literature that have been seen to impact the patient journey or patient care when receiving an unlicensed medicine in the UK. Semi-structured interviews were conducted with community pharmacy staff members (community pharmacists and community pharmacy technicians), prescribers (from within primary and secondary care), and patients (or the parents or carers of those) receiving unlicensed 'special' medicines. Analysis identified key areas where delays or disruption may occur and provides an insight into the views and experiences of those who prescribe, obtain, supply or receive unlicensed 'special' medicines in Wales.

The findings highlight that there is a lack of consistency in the definitions provided for unlicensed medicines and the associated terminology, not only within the literature but also across guidance documents. The lack of consistency was reflected in the limited understanding of all participant groups around what unlicensed 'special' medicines are. The detachment between care settings within the NHS led to multiple areas where delays or disruptions were reported. Overall, the evidence suggests that healthcare professionals and patients would benefit from the creation of consistent guidance and a more integrated healthcare system.

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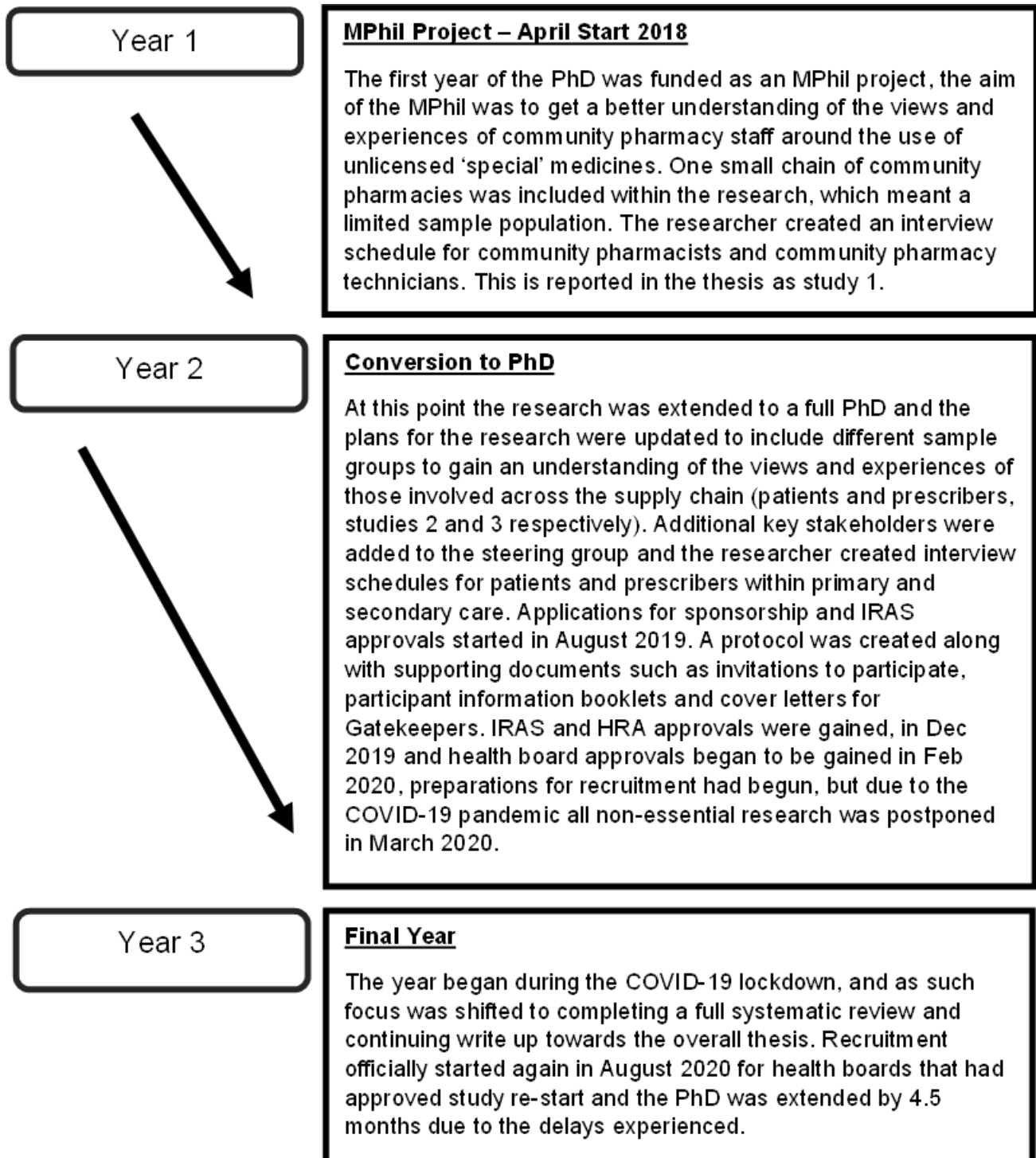
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## 0. Timeline of the PhD\*



\*Timeline of the PhD may differ to the order in which the write up is presented within the thesis

# **1. Introduction**

## **1.1 Overview of chapter**

This chapter consists of an introduction to the thesis research topic and provides a justification for the overall research aims and objectives. Firstly, a brief history around why medicines are licensed for use, along with an explanation of the medicinal licensing process within the United Kingdom (UK) is outlined. This is followed by a description of the differences in how unlicensed medicines are manufactured and supplied, and examples of when unlicensed medicines may be needed to treat patients instead of licensed medicines. As there are multiple types of unlicensed medicines, to ensure understanding and consistency throughout the thesis, the terminology and associated definitions will also be reviewed.

From there, specific factors that can affect treatment success will be presented. This includes how the age of the patient can determine which medicines are used, how side-effects or adverse drug reactions (ADRs) can impact patient care and how patient adherence can impact treatment success.

This is followed by a breakdown of the key stakeholders involved in the different stages of the patient journey including prescribers, community pharmacy staff and patients. The literature is explored in relation to the views and experiences of these stakeholders when unlicensed medicines are used. Lastly, the rationale for the research will be provided along with the aims and objectives of thesis as a whole, as well as the individual aims and objectives of each experimental chapter included in the thesis.

## **1.2 Medicinal licensing in the UK**

### **1.2.1 Why and how medicines are licensed**

In the UK healthcare system, patients can only access medicines either by purchasing them directly or by receiving a prescription from a prescriber. Over the counter (OTC) medicines can be bought in a pharmacy or supermarket and do not require a prescription in order to receive them (NHS 2021a). Pharmacy medicines (P) can be bought or accessed at a pharmacy site, where a registered pharmacist can oversee the sale (RCN 2021). However, prescription only medicines (POM) cannot be bought by the public and can only be accessed through the presentation of a prescription that has been written by a prescriber (MHRA 2020a).

With the most common intervention provided by the National Health Service (NHS) being prescription medicines, accounting for the second largest amount of spending (NHS Digital, 2019), it is a vital aspect of the healthcare system. In primary care between 2018 and 2019, 80.1 million prescriptions were prescribed by General Practitioners (GPs) and dispensed in the community in Wales alone, with a net ingredient cost of £563.2 million (Statistics for Wales, 2019). However, the sale of OTC medicines also accounts for a considerable amount of spending with £2.63 million being spent in Great Britain in 2020 (Statista 2021).

With so many medicinal products being supplied to the public it is important that these treatments are effective and safe. During the late 1950s, the drug thalidomide was provided to pregnant women as a treatment for morning sickness. The drug had a very serious side effect that was not known at the time. This is because medicines were not required to be tested in pregnant animals to assess the potential teratogenic effects, as it was believed that medicines would not be able to cross the placenta (McBride 1961). However, this was not the case and the use of thalidomide led to over 10,000 children being born with serious birth defects (Vergessen 2015). Commonly described as the 'thalidomide disaster' (Ridings 2013), this incident changed the ways in which medicines are regulated around the world (Anderson 2016), with developmental toxicity testing (teratogenicity testing) becoming a requirement and rigorous protocols needing to be followed before a medicine can be marketed (Cook and Fairweather 1968; Kim and Scialli 2011). In the UK, the Medicines Act was created in 1968, which outlined legislation that ensured medicines being sold or supplied to the public must have been subjected to testing to determine the medicine was safe and effective for a specific use and granted a licence to show this (Choonara and Dunne 1998).

Multiple regulations are in place within the UK to ensure medicines being sold or supplied to the public are safe and effective. In line with regulation 46 of the Human Medicines Regulations 2012 (HMR, 2012), medicinal products may be sold or supplied if they have been granted a marketing authorisation or licence. A marketing authorisation provides terms in which the medicine should be used; using the medicine in accordance with this authorisation ensures a level of quality assurance and safety (RPS, 2015). Part of the marketing authorisation is the summary of product characteristics (SPC), which outlines specific details about the indications the medicine can be used for, ranges for the doses that can be given, routes of administration, the age groups the medicine should be used for and any side effects that have been identified at that stage of marketing (RPS 2021).

The Medicines and Healthcare products Regulatory Agency (MHRA) are responsible for the safety and efficacy of all medicinal products and grant a medicine a marketing authorisation

once it has met the required standards of safety and efficacy (MHRA, 2014a). Efficacy has been defined as “*The extent to which an intervention does more good than harm under ideal circumstances*” (Kim, 2013. pg 227). In order for a medicine to be given a marketing authorisation and be classed as a licensed product, the medicine would need to have been put through clinical trials and have been found to be safe and effective for use in the intended population. Clinical trials consist of four phases which allow researchers to determine the correct dosage, identify side-effects, and determine the impact on healthy volunteers as well as the target population (Friedman *et al.*, 2015). Phase 1 aims to identify the highest and lowest doses that are effective in healthy volunteers, Phase 2 is tested on individuals who are suffering from a specific condition with the aim of reviewing efficacy, refining the doses and length of required treatment. Phase 3 involves repeating this process in much larger samples to determine the efficacy and safety for patients and compares the drug to other treatments. Phase 4 continues after licensing has been granted, and records data about the medication overtime to identify any long-term effects (NHS 2019a). However, even after a drug has been through clinical trials, before a medicine can be sold or supplied in the NHS, it must first be appraised to determine prescribing guidance Varnava *et al.*, 2018). In Wales this is done by the National Institute for Health and Clinical Excellence (NICE) or by the All Wales Medicines Strategy Group (AWMSG) (AWTTC 2017).

### **1.2.2 Manufacture and supply of licensed medicines**

Once a medicine has received a marketing authorisation from the MHRA, manufacturers can produce the medicine to be sold and supplied in the UK. The Human Medicines Regulation (2019) give clear regulations for the manufacture of medicines and the processes that must be followed in order to do this as safely as possible. Regulation 14 states that in order to manufacture medicines, a manufacturer’s licence is required, this licence allows specific medicines to be manufactured or, if needed, imported from approved countries. All manufactures must comply with Good Manufacturing Practice (GMP); article 2.6 of the European commission directive (2003 pp.262/23) defines GMP as “*the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use*”. For manufacturers this involves having qualified members of staff to enforce the principles of GMP, having a system in place to ensure quality assurance, maintaining hygiene and equipment standards, keeping detailed records and samples of the medicines created, and regularly taking part in self-inspections (MHRA 2014b). When manufacturers comply with GMP, it ensures that medicines being manufactured throughout the UK will be held to a certain standard and quality and will have records and certifications demonstrating this.

Once these standards have been met and the medicines are manufactured accordingly, only certain organisations and healthcare professionals are allowed to obtain and supply medicines to the public. Regulation 15 of the HMR (2019) covers the requirements of these professionals and states that in order to do this, a wholesale dealer's licence is required. This licence allows the holder to access, store, supply and sell medicines within the UK, and import or export medicines from approved countries. In order to ensure the safety of medicines being supplied all holders of a wholesale dealer's licence must comply with Good Distribution Practice (GDP). The European commission guidelines (2013 pp.343/3) define GDP as the *“part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorised or entitled to supply medicinal products to the public.”* For wholesale dealers this involves maintaining qualified staff members who can enforce GDP, maintaining storage and distribution standards, being able to continually supply a medicine to effectively treat the patient and keeping records about the medicines sold (MHRA 2018).

## **1.3 Unlicensed medicines**

### **1.3.1 Terminology associated with unlicensed medicines**

The term unlicensed medicine encompasses many different types of medicines, including off-label and unlicensed 'special' medicines. Off-label medicines are medicines which have been licensed for a specific use in a specific population but are used in a way not specified by the marketing authorisation in the SPC (MHRA 2014a). Therefore, these medicines are used in an unlicensed manner. Unlicensed 'special' medicines do not have a license and therefore no marketing authorisation, and are made specifically to meet a prescription ordered for individual patients (RPS 2015).

Due to both unlicensed 'special' medicines and off-label medicines being classed as unlicensed medicines, they are often grouped together in the literature despite the differences between them. Mason *et al* (2012), conducted a narrative review of 14 studies and highlighted the different definitions given in the literature and noted how this lack of consistency makes it difficult to compare studies effectively. The narrative synthesis showed clearly how different definitions are often used within the literature, with some studies specifying and defining different types of off-label medicines and others not providing a definition for unlicensed medicines at all. Aronson and Ferner (2017) provided some clarification on the terms in relation to legislation in the UK and suggested that the lack of consistency in the definitions used for unlicensed medicines could lead to confusion for prescribers.



Inconsistencies in the use of definitions associated with unlicensed medicines can cause challenges when creating guidance documents. There are multiple guidance documents available in the UK aimed at helping healthcare professionals to prescribe, access and supply unlicensed 'special' medicines (RPS 2015, RPS 2016). Donovan *et al* (2018), assessed some of the guidance aimed specifically at healthcare professionals that were in use within the UK at the time using the AGREE II tool (Brouwers *et al*, 2010). They reviewed 52 different guidelines and between them found a lack of consistency in the definitions provided. The study showed how healthcare professionals are being provided inconsistent information in guidance documents including differences in how unlicensed medicines are defined, which will inevitably lead to varying perceptions and understanding among healthcare professionals.

For clarification and consistency, table 1.1 contains the terms and definitions that will be used within the thesis with reference to unlicensed medicines, along with the sources they were originally provided in.

**Table 1.1** Definitions selected from the literature and respective sources

<b>Term</b>	<b>Definition</b>	<b>Source</b>
<b>Unlicensed medicines</b>	<i>“The term ‘unlicensed medicine’ is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK”.</i>	General Medical Council. <i>Good practice in prescribing and managing medicines and devices.</i> (GMC 2021, pg.14)
<b>Unlicensed ‘special’ medicine</b>	<i>“A Special is an unlicensed medicine that does not have either a centrally authorised Marketing Authorisation in the European Union or a UK Marketing Authorisation and is manufactured imported or supplied to meet the special clinical needs of an individual patient”.</i>	Royal Pharmaceutical Society. <i>Professional Guidance for the Procurement and Supply of Specials.</i> (RPS 2015, pg.10)
<b>Off-label medicine</b>	<i>“The use of licensed medicines outside their Market Authorisation. The indication may be unlicensed, the dose or the age of the patient may be outside the licence, the route or the method of administration may be outside the licence. In some circumstances, the product may require unlicensed reformulation before administration”.</i>	Wales.nhs.uk <i>Policy For The Use Of Unlicensed Medicines And Medicines Used Outside Their Market Authorisation.</i> (NHS 2010, pg.3)

### **1.3.2 Need for the use of unlicensed medicines**

There are many cases where an unlicensed medicine may be the most suitable treatment for a patient. Regulation 46 of the HMR (2012) states that medicines being supplied to the public must have been granted a UK marketing authorisation or a license that ensures it has met the safety and efficacy standards held by the MHRA (MHRA 2014a). However, when determining a suitable treatment for a patient, certain circumstances may arise in which there is no licensed medicine available that meets the patient’s individual clinical needs.

Regulation 167 of the HMR outlines the exceptions in which a medicine can be supplied without a license. It states that a medicine may be supplied without a marketing authorisation only if “*the medicine is supplied as an unsolicited order*”, is ordered specifically by a healthcare professional, or if the medicine is being created to treat an individual's clinical needs (HMR 2012).

Uses for unlicensed ‘special’ medicines and off-label medicines include those who suffer from rare diseases (Dani, Murray and Razvi 2013), those unable to take a licensed medicine, for example patients with dysphagia (Stone 2014), or those who are allergic to specific excipients (APSM 2019). When licensed medicines are altered in any way, such as when capsules are opened or when tablets are crushed, this is also considered an unlicensed use (Clifton 2012). Unlicensed medicines are used to treat multiple different population groups however, often they are used to treat children and the elderly as medicines are not typically licensed within these age groups (Hilmer and Gazarian 2008). In these cases, doses are determined by scaling down adult doses based on body weight for children (Johnson *et al.*, 2007) and the elderly (BNF 2021a).

Unlicensed medicines are used frequently worldwide, as highlighted by many systematic reviews which have identified the ongoing use of unlicensed medicines across many countries (Conroy *et al.*, 2000; Di Paolo *et al.*, 2006; Magalhaes *et al.*, 2015). However, the MHRA suggest that unlicensed ‘special’ medicines should only be used when there are no licensed, or off-label alternatives available (MHRA 2014c). The thesis will primarily be looking to explore the use of unlicensed ‘special’ medicines, which do not have a marketing authorisation. However, as unlicensed ‘special’ medicines and off-label medicines are often studied together in the literature (Mason *et al.*, 2012), the researcher acknowledges difficulties may be faced when trying to explore views and experiences around unlicensed ‘special’ medicines without gaining information about off-label medicines. This supports the need for individual studies to be conducted exploring the differences in views and experiences between these types of unlicensed medicines.

### **1.3.3 Manufacture and supply of unlicensed ‘special’ medicines**

In order for a manufacturer to create, import and sell unlicensed ‘special’ medicines in the UK, similarly to licensed products, they must have a manufacturer’s specials license, granted by the MHRA, and are expected to comply with GMP (MHRA, 2014a). However, the actual processes involved in the manufacture of unlicensed ‘special’ medicines differs compared to licensed medicines. Specials can be made either in batches, as is the case for more commonly used medicines, or made extemporaneously as a one-off to meet an individual’s needs. In batch-production, multiple samples of the medicine are available that can be

tested for consistency and quality before being released to the public. Each of these batched medicines are given a certificate of analysis, which outlines the tests it has been subjected to, the results of these tests, the lab where the medicine was originally made and should be signed by a qualified member of staff at the manufacturers site (RPS, 2015). Medicines that are made extemporaneously may not be tested for quality in the same ways as medicines that are manufactured in large batches, this is because there is only one sample of the medicine created at any one time (Conroy and McIntyre, 2005). These medicines are instead given a certificate of conformity. This certificate only assures the medicine was created in line with GMP, that the manufacturers have the required license to do so and again must be signed by a quality control professional at the manufacturers site in order to be released (RPS 2015). As unlicensed 'special' medicines have not been through the rigorous testing of clinical trials and are subjected to a varying degree of safety and quality testing, it has been suggested that specials may pose increased risks to patients (RPS 2016).

Similar to the case of licensed medicines, when selling or supplying specials to the public, a wholesale dealers license is required. Regulation 170 of the HMR state that when an unlicensed 'special' medicine is sold or supplied detailed records including the medication itself, where it was made, where it was sold, and the batch number must be kept for a minimum of 5 years and any adverse reactions should be reported to the licensing authority (HMR 2012). The responsibilities to keep additional records for five years are expected of manufacturers and distributors but also of the healthcare professionals involved in supplying the medicines such as pharmacists. This includes maintaining records about *"the source from which and the date on which the person obtained the product; the person to whom and the date on which the sale or supply was made; the quantity of the sale or supply; the batch number of the batch of that product from which the sale or supply was made; and details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware"* (MHRA 2014a pg.11). For prescribers, the GMC (2021) state that a record should be kept of all unlicensed medicines prescribed, and that when the medicine is not commonly used within practice, prescribers should also record the justification for the prescription.

### **1.3.4 Cost of unlicensed 'special' medicines**

In Wales alone, almost £4m was spent on unlicensed 'special' medicines between June 2015 and June 2016, roughly £1 per member of the population ( Mantzourani 2019). As unlicensed medicines are not manufactured in large quantities like licensed medicines, they are typically more expensive (Griffith 2013), with some researchers estimating unlicensed

medicines costing an average of twelve times as much as licensed medicines (Donovan, Parkin and Wilkes 2015). This estimated 12-fold increase is associated with the costs of producing one-off formulations and quality control procedures that are required when manufacturing unlicensed medicines (Chaplin 2006). The cost of additional procedures will depend on the resources available to each manufacturer and is not easily regulated, meaning that the suppliers can determine the cost of making the medicine.

In the UK, the drug tariff contains a list of commonly used medicines and provides set reimbursement prices the NHS are willing to pay, limiting the amount that pharmacists can claim back (NHS 2021b). The often excessive cost of unlicensed medicines has repeatedly been at the forefront of news headlines over the years (Chaplin 2014, The Times 2018). A new section in the drug tariff was introduced in 2011 as an attempt to reduce the overall costs associated with unlicensed 'special' medicines. The new section VIIB contains some commonly used unlicensed 'special' medicines and provides set prices for reimbursement, which are linked to the actual cost of the medicine, in the hopes of increasing transparency (Griffith 2019). By providing set prices this limits the amount that pharmacists will pay to the supplier, as they will only be reimbursed for a certain amount and can therefore limit how much suppliers can charge. While the introduction of the drug tariff list for unlicensed medicines has been seen to reduce NHS spending on specials from £136m in 2010 to £66m in 2018 (Department of Health and Social Care 2019), not all specials used are listed within the drug tariff, and so in some cases pricing is still determined by the manufacturers or suppliers (Chaplin 2014). The Department of Health and Social Care recognise the benefits of part VIIB of the drug tariff; however, it is highlighted that it only includes non-solid dosage forms, while around £26m or 40% of spending on specials in England is for tablets and capsules (Department of Health and Social Care 2019). This suggests further savings could be achieved in the supply of unlicensed 'special' medicines. Terry *et al* (2012), explored the cost saving benefits of having unlicensed medicines supplied directly from the hospital to children at home, although only 67 medicines were supplied this way, the results highlighted a significant impact on cost with over £23,000 being saved. Once an unlicensed 'special' medicine is to be supplied in the community, the manufacturers or suppliers can determine the cost of their products and hidden costs can be incorporated (Griffith 2013). This can explain the often inconsistent cost of specials between suppliers and why medicines supplied by hospital pharmacies have been found to be much cheaper (Klein, Riley and DasDupta, 2008). The evidence available suggests that the cost of unlicensed medicines remains inconsistent and that there are multiple steps that could be taken to reduce the burden of cost on the NHS.

## 1.4 Factors affecting successful treatment

### 1.4.1 Side effects and adverse drug reactions

Medicines can cure or manage illness, relieve pain, distress, anxiety and improve an individual's quality of life (NHS inform, 2020). However, there are also unintended effects associated with taking medications. A side effect is defined as *“an effect of a drug (or treatment or intervention) that is additional to the main intended effect. It could be good, bad or neutral, and that might depend on the circumstances.”* (NICE 2021a, para 22.). Side effects are common and can be tolerable for patients, or can be more problematic, however every medicine has a list of potential side effects (Robertson 2017). In the worst-case scenarios individuals given medicines with the intention of improving their condition may suffer an ADR, which could be the cause of harm or even death. An adverse drug reaction has been defined as *“an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”* (Edwards and Aronson, 2000, pg.1255).

ADRs are a significant health issue around the world. Patel *et al* (2007), reviewed hospital admissions in England caused by ADRs between 1998 and 2005 and found that they had increased by 45%. A further study showed that between 2008-2015 the number of emergency hospital admissions caused in England as a result of ADRs increased by 53.4% (Veeran and Weiss 2017) showing an ongoing challenge for the NHS. In the UK, healthcare professionals and patients can report suspected ADRs through the Yellow Card Scheme (McLernon *et al.*, 2010). This scheme is used to monitor safety concerns, negative reactions, and can be used to provide warnings about any medicines and medical devices being used, although this is a voluntary process relying on individuals to decide to report incidents (MHRA, 2020b). In Wales alone, 3,192 reports were recorded through the Yellow Card Scheme between 2018-2019 (Yellow Card Centre Wales 2019). However, it is also recognised that adverse reactions are underreported in relation to the use of unlicensed 'special' medicines (Sutherland and Waldek, 2015) so the numbers gained through the yellow card system or gained in studies may not be a true representation of the number of adverse reactions experienced by patients receiving unlicensed medicines.

During clinical trials the potential risks or side-effects of medicines are usually determined. However, these trials follow strict procedures and do not take into account situations where medicines may be used in other ways, such as interactions with other medicines being taken, or variations in the dosage or period of time a patient takes the medicine for, factors that could increase the risks of ADRs once being used in clinical settings (Sultana *et al.*,

2013). When looking at unlicensed 'special' medicines, individual studies conducted in the UK, typically focused on paediatric populations, have reported an association between the use of unlicensed 'special' medicines and an increased likelihood of ADRs (Turner *et al.*, 1999; Bellis *et al.*, 2014). A literature review was conducted looking at 14 studies from multiple countries on the use of unlicensed 'special' medicines in paediatrics, which found that prescription rates were between 0.3% and 35% and the studies reviewed again showed an association between the use of unlicensed medicines and ADRs as well as medication errors (Gore *et al.*, 2017). As this review included studies from a range of countries and showed a large variation in prescription rates, the results do not reflect the use of unlicensed medicines specifically in the UK, however, the findings highlight the common use of unlicensed medicines across the globe and suggest increased risks for paediatric patients receiving unlicensed 'special' medicines.

## **1.4.2 Age related factors**

The suitability and efficacy of a medicine can vary depending on the age of the patient, this is because of the pharmacokinetic and pharmacodynamic changes that occur throughout the stages of life (Fernandez *et al.*, 2011). When medicines are being tested for safety and efficacy in clinical trials, this is usually done in adults aged 18-65 (NHS Foundation Trust, 2016). The doses have therefore not been specifically tested for use in elderly and paediatric populations, which leaves these patients vulnerable to increased risks (Hilmer and Gazarian 2008).

### **1.4.2.1 Elderly patients**

In the elderly, physical changes can impact how effectively a medicine is absorbed, distributed, metabolised and excreted by the body and can therefore lead to increased risks of ADRs (Corsonello *et al.*, 2011). As the testing during clinical trials involves giving the medicine to patients who suffer from a specific condition, the potential risks to elderly patients who may suffer from multiple conditions or require multiple medicines are not taken into account, and therefore the doses which have been tested for safety and efficacy in middle aged adults may not be suitable for elderly patients with more complex clinical needs (Davies and O'mahony 2015). Hames and Wynne (2001) looked at the uses of unlicensed medicines in elderly patients in a hospital setting in the UK and found 84% of participants were prescribed off-label or unlicensed medicines, with many participants receiving an average of two off-label or unlicensed medicines per person. Although the study was only conducted over four weeks and included unlicensed and off-label medicines together, it does show the common use of unlicensed medicines within this age group.

Specific conditions such as dysphagia can lead a person to receiving an unlicensed medicine. Dysphagia is the term used for swallowing difficulties and is common in the UK for the elderly, stroke patients and patients with dementia (Barnett and Parmer 2016). Although dysphagia can be experienced at any age, it is recognised that its prevalence increases with age (Leder and Suiter, 2009, as cited in British Geriatric Society 2018). Difficulty swallowing means that receiving medicines in tablet form may not be practical. In the past medicines have been crushed or capsules opened to manage this, however, doing this may change the pharmacokinetics of the medicine within the body and does not comply with the marketing authorisation (Patel 2016). In these cases, if there are no licensed liquid formulations available, unlicensed liquid formulations can be supplied (Stone 2014).

#### **1.4.2.2 Paediatric patients**

Similar to elderly patients, the pharmacokinetic and pharmacodynamic changes that take place during childhood mean that medicines licensed for adults will not be suitable (Batchelor and Marriott 2013) and difficulties or an unwillingness to swallow tablets in children may also increase the chance of a child receiving an unlicensed medicine (Sareen, Ramphul and Bhatt, 2021). In 2007, the Paediatric regulation was enforced in the European Union (including the UK), that required pharmaceutical companies to conduct studies in children (RCPCH 2018). The regulation (EC) No 1901/2006 aims “*to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorized for use in the paediatric population*” (European Commission 2006, pp.2.). A report was produced by the European commission 10 years after the introduction of the Paediatric regulation that highlighted the positive impact the regulation has had, resulting in over 260 new medicines being authorised for use in children and a 50% increase in the number of clinical trials involving children between 2007 and 2016, although challenges with recruiting children into clinical trials were still acknowledged (European Commission 2017). Despite the progress made there is still a lack of medicines specifically designed and tested for children overall due to ethical reasons, such as the balance between providing children with untested medicines, and involving children in clinical trials that may expose them to risks (Joseph, Craig and Caldwell 2015), or financial and practical reasons, such as challenges recruiting children which can take years to gain the required sample size, or the costs involved in recruiting children from across many sites (Lagler, Hirschfeld and Kindblom, 2021).

Childhood can be split into different age groupings: “*preterm neonate, term neonate, post-term neonate, neonate, infant, child, adolescent*” (BNFc 2022, para 7.). Understanding the pharmacokinetic and pharmacodynamic changes during the stages of childhood can be useful in determining appropriate doses (Anderson 2010). However, there is still a limited



amount of data from clinical trials about these changes throughout childhood. Despite the recognition of the need for clinical trials to allow medicines to be tested and licensed for specific use in children (Elhijazi 2018), the concept of clinical trials for children is often met with reluctance due to concerns from parents and doctors (Joseph *et al.*, 2013). Similarly, as children are less likely to be involved in clinical trials, it follows that there is less information known about the safety and efficacy of medicines within this age group. This lack of knowledge can lead to children experiencing treatment failure or medicines with unknown risks (Joseph *et al.*, 2015).

To explore the use of unlicensed medicines in children, Conroy (2010) reviewed the errors reported from a children's hospital in the UK over two years and found errors that led to moderate harm were significantly more likely to be associated with unlicensed and off-label medicines when compared to licensed medicines. Although this study only took data from one children's hospital, it shows an association between the use of unlicensed medicines and increased risks of prescription and dispensing errors.

A narrative review of the literature found that there may also be some association between the use of off-label and unlicensed 'special' medicines in children and a risk of ADRs, however the author acknowledges the studies included in the review were small and varied in terms of their methods and contained varying definitions for unlicensed medicines (Mason, Primohamed and Nunn 2012). Further research would be needed to understand the risks children face due to the lack of medicines created and tested for children.

### **1.4.3 Adherence related factors**

Medicines are most effective when patients adhere to the treatment schedule agreed. However, this is not always the case, and non-adherence can lead to worsening health, treatment failure and even death (Jimmy and Jose 2011). A lack of adherence has been recognised by the World Health Organisation (WHO) as a global problem, with adherence for chronic conditions averaging around 50% in developed countries (WHO 2003). There are different types of adherence behaviours, for example non-compliance, where the patient doesn't follow the recommendations or schedule of treatment, intentional non-adherence, where the patient chooses to stop taking their medicine, and unintentional non-adherence, where the patient may forget to take the medicine when required (Hazell and Robson 2015). However, the term adherence is preferred over compliance as it implies a more positive process in which the patient can choose to adhere to the treatment schedule they have agreed with a healthcare professional, whereas compliance implies the patient must comply with the decision the healthcare professional has made (Chakrabarti 2014).

Adherence behaviours are well studied within the literature. The necessity-concerns framework (Horne *et al.*, 1999) suggests that individuals' beliefs about the perceived necessity of receiving the medicines, and the concerns associated with the medicine itself, can be used as a predictor of adherence, and suggests that patients perform a risk-benefit analysis when they are given a medication that determines their adherence behaviour. This was further supported by Horne *et al* (2013), who conducted a meta-analysis of 94 studies looking at patients who were receiving medication for long-term conditions using the Beliefs about Medicines Questionnaire (BMQ), and found an association between medical adherence and perceived need as well as fewer concerns related to the medicines. The meta-analysis included a large number of studies which helps to support the validity of the necessity-concerns framework and since then, further studies have also found the framework to be correlated with adherence behaviours in a range of conditions (Foot *et al.*, 2016).

The perception of safety when receiving medicines is clearly of great importance for patients in relation to medical adherence and can be an issue at any age. When looking specifically at elderly patients in the USA aged 65 and over, Unni and Farris (2011) used an online survey and gained results from 1,061 respondents who were using Medicare (a private health insurance programme). The findings showed that concerns about the medication were significantly related to reports of forgetting to take medicine or being careless, highlighting unintentional non-adherence. Although the authors recognise the results may not be generalisable, results show the importance of addressing these concerns at all ages, and an insight into the perceptions around unintentional non-adherence. Similar findings, that beliefs had an impact on intentional and unintentional non-adherence, were found in Germany when looking at the views of 309 elderly patients with multiple illnesses (Schuz *et al.*, 2011).

The perceptions patients form about their medication can be related to how much they know and understand about it, that is why it is important to have a good level of health literacy. Health literacy is defined by WHO (2022, para 1.) as referring "*to the personal characteristics and social resources needed for individuals and communities to access, understand, appraise and use information and services to make decisions about health*". Poor health literacy has been identified as a problem in the UK. Rowlands *et al* (2015) assessed the skills necessary to understand 64 examples of healthcare materials used in the UK and compared this to results of a survey with 4,767 members of the public in England. It was found that up to 61% of participants did not meet the literacy and numeracy standards to understand the healthcare materials. Although the study used survey data from another

study conducted in 2011, it reiterates that health literacy is lacking in the general population in the UK in relation to the actual healthcare materials being supplied.

When exploring the impact of health literacy on adherence, a meta-analysis of 48 articles, showed that patients with low levels of health literacy had a 14% increased risk of non-adherence (Miller 2016). The meta-analysis shows that this relationship is seen across the globe and again highlights the role of health literacy in adherence. With low levels of health literacy, a positive relationship with a healthcare professional can make a patient feel more at ease about their condition, their treatment and their choices moving forward. Studies have found that physicians can impact non-adherence depending on the quality of the communication they had (Brown and Brussel 2011). In the UK, a study exploring the impact of community pharmacists giving advice, information and reassurance to patients found that those who received the intervention (255 participants) reported significantly lower levels of non-adherence and medicine related problems than the control group (237 participants) (Clifford *et al.*, 2006). The sample only included patients receiving medicines within the community in England but showed the impact good quality communication with a healthcare professional can have on adherence and treatment success. However, it is not just the communication but also the perceived relationship with a healthcare professional that can impact patient adherence. A European public survey with 45,700 participants from 24 countries found that patients who felt they were treated equally and involved in the decision-making process were more likely to adhere to the treatment schedule (Stavropoulou 2011). The results highlight the importance of a patient-centered approach and shared decision making.

Although much is understood about adherence behaviours and the factors that can impact it, to the author's knowledge there are no studies looking at adherence behaviours for those patients specifically receiving unlicensed 'special' medicines. Further research is needed to gain an insight into the perceived need and concerns of patients receiving unlicensed 'special' medicines to understand the impact on adherence behaviours compared to when receiving licensed medicines.

## **1.5 Key stakeholders in the stages of the patient journey**

To better understand how unlicensed 'special' medicines are used throughout the UK healthcare system, we must first have an understanding of the different roles and responsibilities healthcare professionals hold across the supply chain. Exploring the views and experiences of the healthcare professionals who prescribe, obtain and supply

unlicensed medicines can help to identify areas where challenges may be faced, and how practice may be impacted.

### **1.5.1 Prescribers**

There are many different healthcare professionals who can prescribe unlicensed medicines in the UK, including doctors within primary and secondary care, pharmacist independent prescribers, nurse independent prescribers, and supplementary prescribers (PSNC 2020).

In the UK, all health care professionals, including those that are prescribers, are required to register with a relevant regulatory body: doctors are required to register with the General Medical Council (GMC), pharmacists with the General Pharmaceutical Council (GPhC) nurses with the Nursing Medical Council (NMC) and supplementary prescribers with the Health and Care Professions Council (HCPC). Each Council provides some guidance around the use of unlicensed medicines or advice on where guidance can be found. The GMC (2021) state that when prescribing medicines, the prescriber is responsible for this and therefore should be able to justify their decision-making process and this is no different when prescribing unlicensed medicines. However, the responsibility associated with prescribing unlicensed, or off-label medicines may be greater than when prescribing licensed medicines, and prescribers are encouraged to consider the risks associated with using medicines that aren't licensed, or in a way not specified on the marketing authorisation (MHRA 2014c).

The RPS (2016 pg.6-11) have published guidance on prescribing unlicensed 'special' medicines, and outline five key principles for prescribers to consider when deciding to prescribe. These are:

- “1. Establish the optimal treatment for the patient.*
- 2. Understand the patient's experience and make a shared decision.*
- 3. Identify medicines and preparations.*
- 4. Monitor and review.*
- 5. Ensure effective prescribing governance”.*

The GMC also provide some specific guidance on what prescribers should do when deciding to prescribe an unlicensed medicine. This includes being assured the medicine has enough evidence or use to show it is safe and effective, taking responsibility for the prescription and patient care or ensuring another doctor can, and to maintain clear records of the medicines prescribed including the reasons for the use of an unlicensed medicine (GMC 2021). Similar guidance is also provided by other regulatory bodies such as the NMC (2010) and the HCPC

who refer to the MHRA guidance in relation to the use of unlicensed medicines (HCPC 2022). Although there is guidance available and detailed steps prescribers should take when deciding to prescribe an unlicensed medicine for a patient it may not be as simple as it seems, as prescribers within different settings may have a range of influences when it comes to prescribing and may follow different decision making processes.

### **1.5.1.1 Non-medical prescribers**

Non-medical prescribing was introduced in the UK in 1992. It allowed health care professionals other than doctors or dentists to prescribe medicines (Cope, Abuzour and Tully 2016), after completing additional training post-registration. Non-medical prescribers (NMPs) can include independent or supplementary prescribers such as nurses or pharmacists who can prescribe licensed and unlicensed medicines, and physiotherapists, therapeutic radiographers, podiatrists and paramedics who can prescribe licensed and off-label medicines (NICE 2022). Independent prescribers are responsible for making clinical decisions around assessment and diagnosis for patients and therefore independently prescribe medicines based on these decisions, whereas supplementary prescribers practise more '*dependent prescribing*' where diagnosis would have been determined by a doctor and involves more of a partnership between the doctor and supplementary prescriber to follow a pre-specified clinical plan for the patient (Courtenay and Griffiths 2021 pg.4). Evidence had suggested that non-medical prescribing has been implemented across Wales, with prescribers working in a range of roles and care settings, although the uptake has been reported to be inconsistent with more non-medical prescribers working within secondary care (Courtenay *et al* 2017). However, a more recent study has found that between 2011-2021 non-medical prescribing had increased in primary care by 430% (Deslandes *et al* 2022), suggesting the uptake of non-medical prescribing continues to grow with time. Despite this, medical prescribing continues to be more common with around 300,000 doctors registered across the UK in 2020 (Michas, 2021). Although the number of NMPs are not regularly reported in the UK (Anderson *et al*, 2021), in England it was estimated there were around 58,000 NMPs in 2016 (Cope, Abuzour and Tully 2016).

Despite some non-medical prescribers being able to prescribe unlicensed or off-label medicines, they are limited by their scope of practice. The scope of practice is defined by the HCPC as "*the areas in which a registrant has the knowledge, skills and experience necessary to practise safely and effectively*" (HCPC 2016 pg.13). During their post-registration training, NMPs focus on one therapeutic area as their scope of practice and gain confidence in dealing with patients who present with conditions and symptoms within that area. Even within their scope of practice, training concentrates on published guidance for prescribing, and unlicensed medicines are not routinely included. It is anticipated that NMPs

will widen their scope of practice with experience, but this is a slow process and official guidance has been lacking. For example, the RPS has only recently published guidance for pharmacist independent prescribers on expanding their scope of practice (RPS 2022a). The number of medicines prescribed by medical prescribers is also far greater than those prescribed by non-medical prescribers.

In Wales during the 2017-2018 financial year, non-medical and medical prescribing accounted for approximately 1.4 million items compared to 79 million items respectively. In the 2021-2022 financial year, non-medical prescribing accounted for just under 2.4 million items compared to over 81 million items originating from GP and hospital prescribing (Mantzourani 2022). This shows that despite the increase in non-medical prescribing, medical prescribing remains more common and is accountable for the majority of prescribing in Wales. As such, non-medical prescribers may have less experience and confidence in prescribing unlicensed medicines therefore the thesis will focus on the views and experiences of GPs and secondary care doctors as medical prescribers, as it is expected that they will have more experience prescribing unlicensed medicines.

#### **1.5.1.2 Hospital prescribers**

Multiple factors can impact prescribing decisions in practice, that are not described or addressed in the guidance, for example the impact of working with a team of colleagues. Lewis and Tully (2009) conducted interviews with 48 doctors from four hospitals and found that junior doctors had reported how they were uncertain of the prescribing decisions of more senior doctors which resulted in discomfort when prescribing following their suggestions. Doctors also reported experiencing pressure from the nursing staff to prescribe in certain cases. Overall doctors described prescribing as a method of maintaining team relationships even if it meant not following the hospital regulations. The study was not specifically looking at the prescription of unlicensed medicines however, the results highlight the complexities involved in the act of prescribing and how pressures to prescribe in certain ways may be present within hospitals.

This is supported by a study conducted in 2012 where Ross *et al* explored who actually makes the decision to prescribe for inpatients within hospitals. The results showed that junior doctors prescribed most of the prescriptions but that usually they were not the doctors who made the prescribing decisions. The authors raise the importance of understanding who actually decides to prescribe medicines and the potential for junior doctors to be held accountable for prescription errors that they did not make. As a result of these complex social and professional interactions, prescribers may be held responsible for medicines they

have prescribed but did not make the decision to prescribe, and a lack of communication about the justification when prescribing could explain the discomfort felt by junior doctors.

However, it is not just the healthcare team that can influence prescription decision making processes. Lewis and Tully (2011) found that the patients themselves could cause pressure on hospital prescribers and that of the 48 doctors interviewed, nearly half reported prescribing the medicine the patient wanted despite feeling it was not appropriate. This was done to maintain the relationship with the patient or reduce conflicts within the wards. The findings outline multiple external factors that can impact hospital prescribers' decisions to supply medicines and highlights the complexity of the prescribing behaviour.

### **1.5.1.3 General Practitioners**

General Practitioners or GPs hold many responsibilities, which include treating patients in the community for common conditions and referring patients to hospital or specialist care for further treatment (NHS 2021c). GPs have the authority to prescribe licensed and unlicensed 'special' medicines but are also required to continue prescriptions for licensed and unlicensed 'special' medicines that have been previously initiated in secondary care.

As with prescribers in secondary care, GPs are held accountable for the medicines they prescribe, and this includes when the prescription was initiated by another healthcare professional. Due to this, the GMC (2019) suggest that GPs must be sure the medicines they are being asked to prescribe are safe and suitable for the patient. In order to support this, it has been suggested that when prescribing unusual or unfamiliar medicines, full information should be provided to GPs to ensure they feel competent to prescribe (NHS 2018).

However, GPs like hospital prescribers, have also been found to be influenced by many factors. Carter, Chapman and Waston (2021) conducted semi-structured interviews with GPs, nurses and pharmacists and the results showed that the local or national guidelines available, such as NICE guidelines, influenced prescribing decisions. The individual experience of prescribers was also reported to impact prescribing and individuals within the organisation who held specific knowledge about a speciality provided guidance to other prescribers. It was also noted that the patient characteristics had an influence on prescribing, with prescribers providing medicines that could be bought over the counter to patients who were perceived to not be able to afford them and asking patients to buy the medicines themselves in wealthier areas. Although the study only explored the views of six GPs and 11 non-medical independent prescribers and did not focus on the use of unlicensed medicines, the results highlight a range of factors that were seen to impact prescribing and again reflect a complex process involved in decision-making.

Further prescribing influences were reported by Grant, Sullivan and Dowell (2013), who conducted an ethnographic study involving three general practices, and found that two practices outlined macro and micro factors that impacted prescribing. The macro factors involved gaining information from the available evidence for the use of the medicine for the specific condition and considered policy, whereas the micro decisions involved considering the patient views and perspectives. Interestingly, the one general practice that was ranked as low prescribing quality, only considered the micro factors when prescribing. Although the study was conducted in Scotland and therefore may not be representative of general practices across the UK, the results highlight a balance that is needed between prescribers being influenced by the current policies and available evidence, and by the patient views, circumstances, and individual clinical need.

Overall, making the decision to prescribe a medicine can be a complex process with multiple influencing factors. Although many of the studies discussed above are not specifically focussed on the use of unlicensed medicines, they highlight important findings around who prescribes medicines, and what factors can affect this.

#### **1.5.1.4 Prescribers' views and experiences around the use of unlicensed medicines**

There is a limited amount of evidence from within the UK that explores the views and experiences of prescribers around the use of unlicensed medicines. Donovan *et al* (2016), conducted interviews with a range of healthcare professionals and patients. The prescribers highlighted a lack of information and training for understanding what unlicensed medicines are, and the results highlighted healthcare professionals within primary care were more aware of the cost implications than healthcare professionals in secondary care, suggesting variations in awareness among healthcare professionals around not only what unlicensed medicines are, but also the implication on cost.

Mukattash *et al* (2011), conducted a survey with GPs, hospital consultants, community pharmacists and paediatric nurses, to explore their views around the use of unlicensed medicines in children. The results again showed varying levels of awareness of the different types of unlicensed medicines across settings, with consultants being more familiar with the term off-label medicines and community pharmacists being more familiar with the term unlicensed medicines. Another key finding was that concerns around the safety and efficacy of unlicensed medicines were also reported to vary across settings with GPs and community pharmacists reporting more concerns than secondary care paediatric consultants and nurses. This highlights the varying perceptions of acceptability around the use of unlicensed medicines across care settings.



Prescriber concerns have also been reported by Chisholm (2012) who distributed a questionnaire with 249 prescribers responding from primary and secondary care, and found specific concerns related to the safety of the medicines, their legal responsibilities associated with prescribing medicines and a lack of familiarity with the GMC guidance. These concerns could have the potential to impact practice if prescribers lack the confidence to prescribe unlicensed medicines.

When looking at specific prescribing groups, Howell and Madej (1999) explored the views of members at the Obstetric Anaesthetists Association using an interactive response system. The responses highlighted that although aware of the use of unlicensed medicines, the specialist group lacked awareness on specific indications for the use of some medicines resulting in the unlicensed use of a medicine that was not recommended by the manufacturer. The participants also expressed a desire for more guidance from the OAA, showing a lack of confidence even in specialised healthcare professionals.

When exploring GP experiences, Wong *et al* (2006) conducted interviews with 15 GPs who had previously been found to refuse prescriptions for unlicensed medicines, to explore the reasons for this. The GPs reported a lack of experience and information available to them, concerns around their responsibilities and specific issues such as the cost of the medicine or the medicine being outside of the prescribing guidance. Although the study was only conducted with a relatively small number of GPs, the results highlight how the lack of awareness and concerns prescribers have, can directly impact the patient and disrupt continuity across care settings. Crowe, Tully and Cantrill (2009) explored the factors that influence GP prescribing of specialist drugs by conducting interviews with a range of primary care healthcare professionals. As described above when exploring influences with licensed medicines, the results showed how the individual GP experience, or interests would influence prescribing of specialist medicines. Other factors were also reported such as the influence of cost or advisory lists, the amount of information received from secondary care with the prescription and also patient convenience. These results highlight and support that when prescribing unlicensed medicines there are macro and micro level factors that can influence prescribing and raises the importance of prescriber awareness of what unlicensed medicines are, and an understanding of what indications they should be used for in relation to having the confidence to prescribe specialist medicines.

### **1.5.2 Community pharmacy staff**

The role of a community pharmacist has changed dramatically over the years from simply dispensing medicines to a more patient focussed role (Tucker 2018). There are 712 community pharmacies in Wales alone (as of March 2021)(Welsh Government 2021a), and

community pharmacy staff are the last point of contact for patients receiving unlicensed 'special' medicines in the community, and as with other healthcare professionals involved, hold a level of responsibility for this. Once an unlicensed medicine has been prescribed to a patient in the community, it is the responsibility of the community pharmacy team to obtain and supply the medicine and ensure treatment can continue.

When provided with a prescription for an unlicensed medicine the pharmacist is responsible for ensuring that the medicine is only provided if there are no suitable licensed alternatives and to source a cost-effective supply (NHS 2012). Community pharmacists hold many other responsibilities associated with obtaining and supplying unlicensed medicines, this includes ensuring the medicine is the most suitable for the patient, ensuring that the side effects and expiry dates are present on the dispensing label, and providing advice to patients when there is no patient information leaflet (NHS 2019b).

The RPS (2015 pg.5-9) outline that the pharmacist shares the responsibility with the prescriber when supplying an unlicensed medicine to a patient and outline five key principles to guide pharmacists when procuring and supplying unlicensed 'special' medicines. These are:

- “1. Establish the optimal treatment for the patient.*
- 2. Understand the patient’s experience and make a shared decision.*
- 3. Identify a preparation and supplier.*
- 4. Monitor the patient and review the need for a special.*
- 5. Ensure effective governance is in place ”.*

#### **1.5.2.1 Community pharmacy views and experiences around the use of unlicensed 'special' medicines.**

There is a limited amount of literature exploring the views and experiences of community pharmacists on the use of unlicensed 'special' medicines in the UK. The available evidence shows that over 70% of 482 community pharmacists involved in a questionnaire study were familiar with the use of off-label medicines and that the British National Formulary (BNF) was a primary source of information for them (Stewart *et al.*, 2007).

As mentioned above, Mukattash *et al* (2011) found that community pharmacists reported concerns about the safety and efficacy of unlicensed medicines. Although gained from the interviews with parents of patients who receive unlicensed medicines, multiple studies have described pharmacy issues with the community pharmacy staff being unable to find a manufacturer to obtain the specific unlicensed medicine required, which led to delays (Wong

*et al.*, 2006; Husain, Davies and Tomlin 2017). The results suggest that although community pharmacists are aware of the use of unlicensed and off-label medicines, they may still have concerns over their uses and may face challenges when obtaining and supplying these medicines.

Overall, the inconsistencies identified in the guidance available to healthcare professionals when prescribing and supplying unlicensed medicines (Donovan *et al.*, 2018) will inevitably lead to differing perceptions and understanding among healthcare professionals. This is reflected in the literature where differing definitions are used across studies and varying levels of awareness of what unlicensed medicines are, and acceptability in relation to the use of unlicensed medicines, were reported by healthcare professionals across settings. This variation in awareness of what unlicensed medicines are and acceptability of their use, could have implications on practice when healthcare professionals across settings are required to work together when patients are transferred.

### **1.5.3 Transfer of care**

Unlicensed medicines can be prescribed within secondary care and continued into the community after discharge, or initiated in primary care. This requires multiple care settings to work together to ensure the continuity of treatment and results in multiple healthcare professionals holding responsibility for the decision-making process of whether the medicine is prescribed or supplied at different stages of the patient journey.

Transfer of care between clinical settings has been identified by the WHO as holding risks for patients as the process involves co-ordination across settings (WHO 2016) and increased risks of medication errors at the point of transition (WHO 2019a). A systematic review by Alqenae, Steinke and Keers (2020) which included 54 studies from 26 countries including the UK, found that the average rate of medication errors for adults after discharge from hospital was 53%, highlighting a significant risk to patients around the world.

One way of attempting to minimise medication errors, improve medication safety during transfer of care, and improve the quality of communication between healthcare professionals was the introduction of the Discharge Medicines Review service (DMR) in Wales in 2011 (Hodson *et al.*, 2014). The DMR is a two-part intervention conducted by community pharmacists aimed at improving transfer of care by ensuring medication changes are accurately recorded and acted upon in the community and supporting the patient to adhere to medications (CPW 2021). The benefit of the DMR service to patient care has been reported by Mantzourani *et al* (2020) who found a significant reduction in the risk of hospital readmissions for those who used the service. It was also the only advanced service that was

maintained in community pharmacies by the Welsh Government during the Covid-19 global pandemic (Welsh Government 2020). Despite evidence that providing community pharmacy staff with clinical information around discharge can improve continuity and reduce hospital admissions (Wilcock *et al.*, 2019), it has been reported the amount of information community pharmacies receive about prescriptions is inconsistent (Urban *et al.*, 2013) and the DMR along with similar services, do not typically provide reasons for medication changes and there is no specific requirement to state the licensing status of the medicines.

Issues experienced around the transfer of care for unlicensed medicines have been reported by Donovan *et al* (2021) where primary care prescribers acknowledge the potential for mistakes due to the lack of familiarity with the medicines prescribed. Moreover, when unlicensed medicines are initiated by specialists in secondary care there is no established care pathway to inform the primary care prescriber or community pharmacy about the clinical reasoning for this. The lack of familiarity with certain unlicensed medicines and the lack of information received with prescriptions for unlicensed medicines across settings has been reported as a cause of GPs deciding not to continue a prescription (Wong *et al.*, 2006). As the GMC guidance states that GPs should be sure the medicine prescribed is safe and effective before continuing to prescribe (GMC 2021), deciding against continuing a prescription is a justifiable and understandable outcome for GPs who are asked to prescribe unfamiliar unlicensed 'special' medicines or unlicensed 'special' medicines with limited evidence. However, this has a direct impact on the patient experience and care if their local GP has decided not to continue a prescription for an unlicensed 'special' medicine they had previously been receiving from secondary care and could lead to delays or disruption.

#### **1.5.4 Patient and public views and experiences around the use of unlicensed medicines**

In order to improve the overall patient experience, we must first understand the views of the patients who receive unlicensed medicines and explore the experiences they have faced when trying to access their medicines.

##### **1.5.4.1 Views of the public**

In the UK, Chisholm (2012) conducted online questionnaires with 500 members of the public and found that 63% reported a lack of awareness around the medicinal licensing process in general, with 53% believing medicines could only be supplied for specific uses in approved conditions. As the study included members of the general public, awareness levels for patients receiving unlicensed medicines in the UK may differ but the findings highlight that the general public have a lack of awareness around the use of unlicensed medicines.

Mukattash *et al* (2008) also found a lack of awareness in the general public on the use of unlicensed medicines in children and found that only 1.8% of participants felt that medicines for children were not safe, however this increased to 64.2% after being informed about the use of unlicensed medicines within this age group. Mukattash *et al* (2012) also explored the views of children in the UK and conducted focus groups with 123 pupils aged 10-16, they discovered that children found the use of unlicensed medicines to be unsafe and acknowledged that although parents should be informed, this could influence adherence to unlicensed medicines due to parental concerns around safety. The study used the term unlicensed medicines to encompass both unlicensed and off-label medicines, so the results do not reflect specific views on the different types of medicines, and used a relatively small sample, but does show that children are able to determine and understand the risks associated with using unlicensed medicines and understood the need for medicines to be licensed for use in children.

The concerns reported in the literature related to the unlicensed status of medicines by the general public suggests that there may be issues with adherence, although to the researcher's knowledge, there are no studies exploring this directly. Further research is needed to explore patients' perceptions of need and concerns to better understand their views around unlicensed medicines and explore adherence behaviours.

#### **1.5.4.2 Views and experiences of parents, carers, or patients**

As described in 1.4.3, unlicensed 'special' medicines are often prescribed to children as clinical trials are not typically conducted in children, resulting in less available licensed medicines for paediatric patients. The literature available therefore reflects this, and multiple studies have focused on exploring the views and experiences of parent or carers when accessing unlicensed 'special' medicines for their children. In a systematic review, Balan, Hassali and Mak (2015) found three studies that explored the views of parents in relation to the use of unlicensed and off-label medicines and found that awareness within this group was relatively low. One study reported how 73% of parents thought the use of off-label medicines was illegal (Bang *et al.*, 2014), another found that 86% of parents were unaware about the use of unlicensed medicines (Mukattash *et al.*, 2008), and the final study highlighted how 20% of parents of healthy children and 9% of parents of children with chronic conditions would refuse treatment with an off-label medicine (Lenk *et al.*, 2009). However, as with other reviews in this area, the terms unlicensed and off-label are often grouped together in the literature, with two of the studies focused on off-label medicines and one looking at off-label and unlicensed medicines, making it difficult to determine specifically what the parents were and weren't aware of and making it difficult to compare the studies. The review also included studies from multiple countries (India, Northern Ireland and

Germany respectively) so does not reflect the awareness of patients or the public specifically in the UK, but shows how a lack of awareness about the use of unlicensed medicines has been seen within the general public across many countries.

This is further supported by findings in India (Saiyed, Prajapati and Shah, 2015) where questionnaires of 407 parents revealed that 89.9% were unaware of off-label medicines, and in Croatia (Curkovic and Gorjanski 2018) where questionnaires of 1,300 parents found that 96.3% had no knowledge of off-label medicines, and once informed 54.5% of parents reported they would not accept an off-label medicine for their children. The studies were focused on off-label medicines and therefore may not be representative of the views of parents around unlicensed medicines, but does show a lack of awareness in many countries around the different licensing status' of medicines used for children, and further supports parental concerns and a lack of acceptability around the use of medicines not specifically licensed for use in paediatric populations.

Mukattash *et al* (2019) explored the views of parents around the use of off-label and unlicensed medicines and conducted online questionnaires across the Arab nation, of the 4,740 participants gained, 55.2% had no knowledge about the use of unlicensed medicines and 65.3 % reported thinking that medicines used for children were very safe, this significantly decreased to just 35.4% once being informed about the use of off-label and unlicensed medicines. Again, this study grouped the terms unlicensed and off-label but highlights a lack of awareness and understanding and shows how further knowledge can lead to increased concerns, suggesting implications for non-adherence in relation to the use of unlicensed medicines.

As parents are responsible for consenting to their child receiving an unlicensed 'special' medicine, an increase in awareness around the licensing process and implications of receiving an unlicensed medicine is needed for parents to be able to provide fully informed consent. In some of the guidance documents mentioned above, it is suggested that patients should be informed when a prescriber initiates the use of an unlicensed medicine (NICE 2021b). However the GMC (2021) suggest that it may not be necessary to "*draw attention*" to the fact the medicine is unlicensed as it may cause concerns to the patients. This lack of clarity about informing the patient fully could be one reason there appears to be a lack of awareness in the general public.

When exploring the actual experiences related to receiving an unlicensed medicine in the UK, there is limited existing research, with studies again focusing on paediatric patients and exploring the views and experiences of the parents and carers in relation to accessing unlicensed medicines for their children. In the UK, Wong *et al* (2006) conducted telephone

interviews with 216 parents and carers of children aged 5 months – 18 years and found that around a third of participants had experienced difficulties accessing their medicines after discharge, this was due to GPs deciding not to continue to the prescription that had been initiated in secondary care, or community pharmacies unable to access the correct formulations. Like much of the literature around unlicensed medicines, this study only included parents of paediatric patients, so does not give a full look at the accessibility of unlicensed medicines for all ages, however highlights a serious problem with supply issues when accessing unlicensed medicines in the community for paediatric patients.

These issues were also reported more recently by carers in London (Husain, Davies and Tomlin 2017), where parents described how in order to manage the delays and challenges faced, they felt as if they had to play a specific role and take action to ensure the successful supply of their child's medication, this included planning and organising the process of ordering and receiving the unlicensed medicines and increased interaction with GPs, pharmacists and other healthcare professionals. This perceived need to take on responsibility in order to successfully access their children's medicines led participants to feel increased levels of stress and concern. Although the study only included a small sample of just 15 participants, it highlights some important experiences of parents who actually access unlicensed medicines in the community and some of the challenges being faced.

The literature helps to highlight a lack of awareness around the use of unlicensed medicines not only in the general public but also for patients or carers of patients. The literature also shows increased concerns, and some specific issues that have been experienced when trying to access unlicensed medicines for patients, however the amount of literature exploring the views of patients actually receiving unlicensed medicines in the UK is limited. Further research is needed to better understand the views and experiences of patients who receive unlicensed 'special' medicines in the UK to identify factors that can impact the patient journey and patient care.

## **1.6 Rationale for research**

This chapter has highlighted that the use of unlicensed 'special' medicines can sometimes involve a complicated process that transfers across care settings and involves multiple healthcare professionals. Although the literature shows the common use of unlicensed medicines across the world, it also highlights a lack of awareness and understanding of healthcare professionals, patients and the general public around what unlicensed medicines are and how they are used. The limited data available from within the UK suggests that patients have experienced issues when trying to access unlicensed medicines after

discharge and that this could be the result of a lack of acceptability among prescribers or a lack of accessibility for community pharmacies. To the researcher's knowledge there are no studies exploring the views and experiences of the healthcare professionals and patients' perspectives around the use of unlicensed 'special' medicines specifically in Wales, where the responsibility for NHS Wales lies within the Welsh Cabinet Secretary for Health and Social Service after devolution. The structure of NHS Wales differs to other areas of the UK. In Wales, care is provided through seven regional health boards, which cover all areas of care across settings for a specific area, and three NHS trusts (NWSSP 2022). In NHS England they do not have integrated health boards in this way and instead care is provided by over 200 NHS trusts (Worthington, 2019). The local health boards in Wales have been in place since 2009 and have aimed to integrate care across settings (Lewis 2015). Over the past few years there has been a continued focus on integrated care systems, and in the plan for 'A Healthier Wales' further integration has been suggested between health and social care (Welsh Government 2021b). As Wales have a pre-existing integrated care system, that has had the time to mature, the issues associated with the use of unlicensed medicines may differ to those identified in other areas of the UK. In England, changes are being made to create a more integrated care system, with a new bill being passed in 2021 and changes to be implemented during 2022 (RPS 2022b). As such, the lessons learned from this thesis could be transferable and used to help inform practice in other areas of the UK. Another key difference is the ongoing prescription charges present in England that were abolished in Wales in 2007. The literature has suggested that this has led to an increase in medicines prescribed as well as a decrease in non-adherence (Groves *et al.*, 2010).

In order to improve the patient experience, we must first have a better understanding of what is actually happening when unlicensed 'special' medicines are prescribed, obtained and supplied to patients from the perspective of those who are involved in this, as this appears to be an under researched area. By understanding the views and experiences of stakeholders involved in the use of unlicensed 'special' medicines the strengths and weaknesses involved in the process can be identified. The researcher aimed to use this information to provide evidence-based suggestions for change, that could be used to improve the patient experience in Wales.

### **1.6.1 Aims and objectives**

The overall aim of the studies in this thesis is to explore the views and experiences of those involved in prescribing, accessing, supplying or receiving unlicensed 'special' medicines, so as to be able to highlight strengths and weaknesses and provide evidence-based suggestions for change that could improve the patient experience in Wales. As the use of



unlicensed medicines can be complex and involve multiple healthcare professionals across care settings, a further objective of the thesis is to explore the impact of the current integrated care systems in Wales on the use of unlicensed medicines. To address the aim, a systematic review and three studies were designed, the individual aims and objectives of each study are outlined below.

#### **1.6.1.1 Systematic review**

**Aim:** The aim of the systematic review was to explore the patient journey and patient care (as defined in chapter 2, see 2.2.1) when receiving an unlicensed medicine in the UK, and to identify the factors that can affect it.

**Research question:** What factors affect the patient journey and care when receiving an unlicensed medicine in the UK?

#### **Objectives:**

- To determine factors that affect the patient journey when accessing and receiving unlicensed medicines in and across different care settings
- To determine factors that affect the continuity of supply of unlicensed medicines in and across care settings
- To determine what patients who receive unlicensed medicines have experienced during the process of being treated
- To determine what healthcare professionals across settings have experienced during the process of prescribing, accessing, and supplying unlicensed medicines that can affect the patient journey
- To determine what factors affect patient care when receiving unlicensed medicines

#### **1.6.1.2 Study 1**

**Aim:** The aim of study 1 was to explore the views and experiences of community pharmacy staff around accessing and supplying unlicensed 'special' medicines.

#### **Objectives:**

- To explore pharmacy staff understanding and awareness of the use of unlicensed 'special' medicines
- To explore pharmacy staff perceptions of acceptability when accessing and supplying unlicensed 'special' medicines

- To explore pharmacy staff experiences related to the accessibility of unlicensed 'special' medicines
- To explore pharmacy staff experiences when supplying unlicensed 'special' medicines

### **1.6.1.3 Study 2**

**Aim:** The aim of study 2 was to explore the views and experiences of patients, or the parents and carers of those who receive unlicensed 'special' medicines.

**Objectives:**

- To investigate patients' understanding of unlicensed 'special' medicines and their use in practice
- To explore patients' perceptions of safety and quality of unlicensed 'special' medicines from different sources
- To investigate patients' experiences around receiving unlicensed 'special' medicines, manufacturing timelines and delay obtaining treatment

### **1.6.1.4 Study 3**

**Aim:** The aim of study 3 was to explore the views and experiences of prescribers in primary and secondary care who have experience of initiating or maintaining therapy with unlicensed 'special' medicines.

**Objectives:**

- To investigate prescribers' understanding of unlicensed 'special' medicines and their use in practice
- To explore prescribers' perceptions of safety and quality of unlicensed 'special' medicines from different sources
- To investigate prescribers' experiences around prescribing unlicensed 'special' medicines, manufacturing timelines and delay obtaining treatment
- To explore prescribers' approach towards initiating or maintaining therapy with an unlicensed 'special' medicine

## **2. Factors affecting the patient journey and patient care when receiving an unlicensed medicine in the UK: A systematic review**

### **2.1 Overview of chapter**

The Introduction and literature review in chapter 1 highlighted a limited amount of evidence on the views and experiences of those involved in prescribing, obtaining, supplying and receiving unlicensed medicines in the United Kingdom (UK). To improve the overall patient experience, there is a need to better understand the patient journey when receiving an unlicensed 'special' medicine in the UK, and to identify the factors that can affect it.

This chapter consists of a systematic review exploring the factors that affect the patient journey and patient care when receiving an unlicensed medicine in the UK. The review does not solely focus on the use of unlicensed 'special' medicines as it has been reported that there is a lack of consistency in the definitions used within the literature, with terms associated with 'specials' such as unlicensed or off-label, often being grouped together (see 1.3.1). In order to gain as much information as possible, the systematic review included any study that mentioned the term unlicensed medicines or specials.

Some background information on what is known about the patient experience and the need and justification for conducting the systematic review is provided in the introduction to the chapter. This is followed by a description of the methods used during the searching, screening and synthesising of the data, with an explanation of how the eligibility criteria and screening criteria were determined. Following this, a detailed description of the results will be provided including individual study commentaries for each of the studies selected for inclusion in the review, and an outline of the analysis methods used. Lastly, a discussion exploring the relationships within the data, some information on the limitations faced while conducting the systematic review, and final conclusions will be presented.

### **2.2 Introduction**

#### **2.2.1 Rationale**

Evidence from across the UK suggests that parents and carers have faced difficulties when trying to access further supplies of an unlicensed medicine after their child had been discharged from hospital, due to either concerns raised by GPs when asked to continue prescriptions, issues with the cost of the medicines, or an inability of community pharmacies to obtain specific formulations (Wong 2006; Husain, Davies and Tomlin 2017). Studies have

been conducted within the UK that explore the views and experiences of those prescribing, supplying and receiving unlicensed medicines, which have revealed concerns from the healthcare professional and public perspectives around the safety of unlicensed medicines (Mukattash *et al.*, 2011; Chisholm 2012). However, there is a limited amount of evidence available, and to the researcher's knowledge none of the studies have a specific focus on the patient journey as a whole and therefore may only identify barriers and facilitators on the use of unlicensed medicines in relation to certain areas of the patient journey.

In order to improve the overall patient experience there is a need to better understand the factors that can affect the patient journey as a whole. This will help to identify areas where issues commonly arise, which can then be targeted for change, while providing the context to allow the researcher to consider the impact any potential changes may have on other aspects of the patient journey. In an effort to gain as much information as possible from the limited literature available, it was decided to conduct a systematic review exploring the factors that affect the patient journey and care when receiving an unlicensed medicine in the UK. A systematic review aims to collect available evidence using specific criteria and strategies, to review the evidence for quality and to synthesise the findings to create reliable results that answer the research question (Chandler *et al.*, 2021). By conducting a systematic review, the researcher hoped to gain a better understanding of the patient journey as a whole and identify factors that can affect it.

The patient journey was considered from the point the first decision to initiate treatment with an unlicensed medicine was made and a prescription was issued in a primary or secondary care setting, to the point at which treatment is supplied through a community pharmacy or ends. Understanding the patient journey could involve collecting information about healthcare professionals' views and decisions to initiate treatment using unlicensed medicines in primary and secondary care, experiences related to the transfer of care across settings, the process and experiences around obtaining or accessing unlicensed medicines by healthcare professionals or patients, and the overall patient care and satisfaction throughout this journey. Patient care relates to the quality of care the patients' received, such as the continuity of care across care settings and any potential risks to safety or adverse reactions experienced.

To ensure the area of interest had not previously been reviewed, prior to developing a protocol for the review, a search was conducted in the Joanna Briggs Institute EBP Database (Joannabriggs.org), the Cochrane library (Cochranelibrary.com 2020) and PROSPERO (PROSPERO 2020); no systematic review on this topic was found. The structure of this chapter was based upon the PRISMA (Preferred Reporting Items for

Systematic review and Meta-Analysis) 2009 checklist (Moher *et al.*, 2009), a 27-item checklist that was used to create a detailed account of the steps taken during the systematic review.

## 2.2.2 Research aim and questions

The aim of the systematic review was to explore the patient journey and patient care when receiving an unlicensed medicine in the UK, and to identify the factors that can affect it.

The mnemonic PICO has been well established within the literature as an effective template when creating research questions for systematic reviews (Schlosser *et al.*, 2007). First introduced by Richardson *et al* (1995), PICO stands for patient/problem, intervention/exposure, comparison and outcomes. However, this tool was developed for use in quantitative reviews and as such has been modified over time to better address different research methods (Methley *et al.*, 2014). As this systematic review aimed to include a range of studies both qualitative and quantitative, but to primarily gain experiential evidence the researcher decided to use the template PICo (population, phenomena of interest, and context)(Munn *et al.*, 2018). To address the aim of the review, a research question and multiple sub questions were created using PICo (Munn *et al.*, 2018).

Population	Those involved in prescribing, accessing, supplying or receiving unlicensed medicines
Interest	Factors that impact the patient journey or care
Context	UK

### Research question

What factors affect the patient journey and care when receiving an unlicensed medicine in the UK?

### Sub questions:

- What factors affect the patient journey when accessing and receiving unlicensed medicines in and across different care settings?
- What factors affect the continuity of supply of unlicensed medicines in and across care settings?
- What have patients who receive unlicensed medicines experienced during the process of being treated?

- What have healthcare professionals across settings experienced during the process of prescribing, obtaining, and supplying unlicensed medicines that can affect the patient journey?
- What factors affect patient care when receiving unlicensed medicines?

## **2.3 Methods**

### **2.3.1 Protocol and registration**

The researcher created a protocol for the systematic review based on the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (Moher *et al.*, 2015) and the PROSPERO protocol template, to improve the quality of the protocol and increase replicability. The protocol was submitted to and registered on the PROSPERO website and given the protocol registration number CRD42020190201.

### **2.3.2 Eligibility criteria**

#### **2.3.2.1 Study designs**

To gain as much information as possible, the researcher included quantitative, qualitative, or mixed method studies related to prescribing, accessing, supplying, or receiving unlicensed medicines within the UK. As grey literature was discussed in the introduction chapter (see chapter 1) and cannot be quality assured in the same way as original research it was not included in the systematic review.

#### **2.3.2.2 Participants**

Participants consisted of multiple population groups. The review included studies that explored the views and experiences of the healthcare professionals who prescribe, access or supply unlicensed medicines, as well as studies that explored patients', parents', carers' and the general public's views and experiences around the use of unlicensed medicines in the UK. No age or other demographic restrictions or filters were used when including participants, so as to gain as much information as possible about the patient journey or views from the perspective of any individual who had experienced or been informed about the use of unlicensed medicines.

#### **2.3.2.3 Phenomena of interest**

The aim of the review was to identify factors that can affect the patient journey and care when receiving an unlicensed medicine in the UK. To explore these phenomena, the researcher aimed to include evidence from the healthcare level (e.g., regulations, guidance, company policies, barriers to supply, perceptions of accessibility and acceptability etc.), or from the individual level (e.g., decision making in prescribing and supplying, experiences with

prescribing, accessing, supplying and receiving unlicensed medicines, or the views and perceptions around these experiences).

#### **2.3.2.4 Setting**

Only studies conducted within the UK were included in the review. More specifically, any studies based in a healthcare setting where unlicensed medicines may be prescribed or supplied were included, or studies where the use of unlicensed medicines by members of the UK public was discussed. Any studies conducted outside of the UK were excluded as the review was focussed on the patient journey specifically in the UK, and different countries may have varying processes involved when accessing and supplying unlicensed medicines, and therefore differing factors that could affect the patient journey. Studies published prior to 1968, when the Medicines Act was put into place and regulations around the use of unlicensed medicines were enforced in the UK, were also excluded from the review.

#### **2.3.2.5 Language**

Only studies presented in English were included in the review. English translations of studies reported in another language, were not included as the focus of the review was on the patient journey specifically in the UK, and it was assumed that this would not be the case in any study originally reported in a language other than English. No filter was used during searching to reduce the likelihood of accidentally removing useful studies from inclusion, but any studies identified that were conducted in another country or reported in another language were removed during round 1 of screening (see 2.3.5).

### **2.3.3 Information sources**

Multiple databases were searched for the review. These were selected based on what would encompass the most relevant information, and by including the main databases reported to produce reliable results, as suggested by Bramer *et al* (2017). Specific databases such as PubMed which contains information from MEDLINE, were not included in the review in order to reduce the number of duplications gained. Databases that contained only systematic reviews such as the Cochrane library, were also excluded as the review aimed to look at original research only and not reviews of multiple studies, and the studies included in reviews should have been collected throughout data collection individually. The databases used were:

Scopus;

OVID EMCARE;

EMBASE;

OVID Medline ALL;

CINAHL (The Cumulative Index to Nursing and Allied Health Literature);

Web of Science;

Joanna Briggs Institute (JBI).

Google Scholar was also searched using keywords to gather any extra data that had not already been identified from the database searches, with the first five pages of results being reviewed to identify any potentially relevant papers.

### 2.3.4 Search strategy

Search terms were developed using an iterative process whereby the researcher conducted multiple scoping searches using combinations of keyword terms and strategies, quickly screened the results for relevance, and then refined the terms for further trials. During the whole process discussions were taking place with supervisors and a subject librarian with experience conducting systematic reviews. Due to the limited amount of research around the use of unlicensed medicines in the UK, scoping searches revealed it was unnecessary to further filter results using keywords such as “patient journey” or “experience” before screening could reasonably begin. No filters were used to limit the search results, to reduce the likelihood of unintentionally filtering out useful resources. The final list of search terms created and used in the review can be seen in table 2.1.

**Table 2.1.** Search terms used for the systematic review: columns and rows represent how boolean operators were used

Search terms	
OR ↓	AND →
	Unlicensed Drug
	Specials Drugs
	Medicine
	Medicines
	Medication
	Medications
	Preparation
	Preparations
	Formulation
Formulations	



As many of the databases selected used differing Boolean and Proximity operators, the search strategies used varied depending on the database. The search strategies that were used to search EMBASE and Scopus along with the number of results gained can be seen below (see table 2.2). The individual search strategies conducted in all other databases can be found in Appendix 1. Slight variations in the search strategies can be seen because Scopus automatically searches for plurals unlike EMBASE, meaning the researcher did not have to run as many searches. However, this resulted in the search term “specials” identifying data that mentioned any variation of the word special, such as specialised or specialist and collecting too many irrelevant sources. To overcome this, the researcher used brackets to conduct keyword searches for the term “specials”. As a consequence, the proximity operator could no longer be used, instead the Boolean operator AND was used for the searches related to specials.

Searches were completed in July 2020 and alerts were set in each database to update the researcher when new results were published. These updates were reviewed along with a final search that was conducted in November 2020 to collect any new research before final synthesis began.

**Table 2.2** Examples of search strategies used in systematic review

<b>OV-D - EMBASE (599)</b>	<b>Scopus (586)</b>
1. unlicensed adj2 drug (364)	1. unlicensed W/2 drug (358 results)
2. unlicensed adj2 drugs (115)	2. unlicensed W/2 medicine (136 results)
3. unlicensed adj2 medicine (47)	3. unlicensed W/2 medication (54 results)
4. unlicensed adj2 medicines (131)	4. unlicensed W/2 preparation (10 results)
5. unlicensed adj2 medication (30)	5. unlicensed W/2 formulation (15 results)  Go into saved searches use toolbar to combine searches
6. unlicensed adj2 medications (37)	6. #1 OR #2 OR #3 OR #4 OR #5 (507 results)
7. unlicensed adj2 formulation (3)	7. {specials} AND drug (56 results)
8. unlicensed adj2 formulations (16)	8. {specials} AND medicine (33 results)
9. unlicensed adj2 preparation (7)	9. {specials} AND medication (6 results)
10. unlicensed adj2 preparations (11)	10 {specials} AND preparation (19 results)
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (593)	11. {specials} AND formulation (14 results)
12. Specials adj2 drug (3)	12. #7 OR #8 OR #9 OR #10 OR #11 (88 results)
13. specials adj2 drugs (0)	13. 6 OR 12 (586)
14. specials adj2 medicine (0)	
15. specials adj2 medicines (10)	
16. specials adj2 medication (0)	
17. specials adj2 medications (1)	
18. specials adj2 formulation (1)	
19. specials adj2 formulations (0)	
20. specials adj2 preparation (0)	
21. specials adj2 preparations {0}	
22. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 (15)	
23. 11 OR 22 (599)	

## **2.3.5 Study selection**

### **2.3.5.1 Data management**

The results of the searches were exported from the databases and transferred into Mendeley®, a reference management software. Using the deduplication tool within the software, over 1000 potential duplicates were initially highlighted. The researcher manually reviewed each potential duplication and the individual corresponding studies, before determining if the duplication was accurate and needed to be removed.

### **2.3.5.2 Selection process**

Following the PRISMA guidance, selection took place in two rounds: rounds 1 and 2.

*Round 1-* Round 1 involved screening the abstracts of the papers identified after the deduplication process, using a specific set of criteria (see figure 2.1). The researcher created the screening criteria for abstracts using a reflective approach which involved creating some initial screening criteria, looking through some of the initial search results to identify specific aspects that needed to be screened out, and using this information to update and finalise the screening criteria. For example, even though results from the search had originally included abstracts that referred to the use of unlicensed medicines when treating animals, it was decided that these would be excluded as the aim of the review was to get a better understanding of patient journey and human experiences around the use of unlicensed medicines. As a result of this, a question within the screening criteria was updated to refer specifically to the use of unlicensed or specials “in relation to human medicines”. Conference and poster abstracts were included at this stage in the hopes of being able to access a full version of the abstract.

### Screening criteria for abstracts

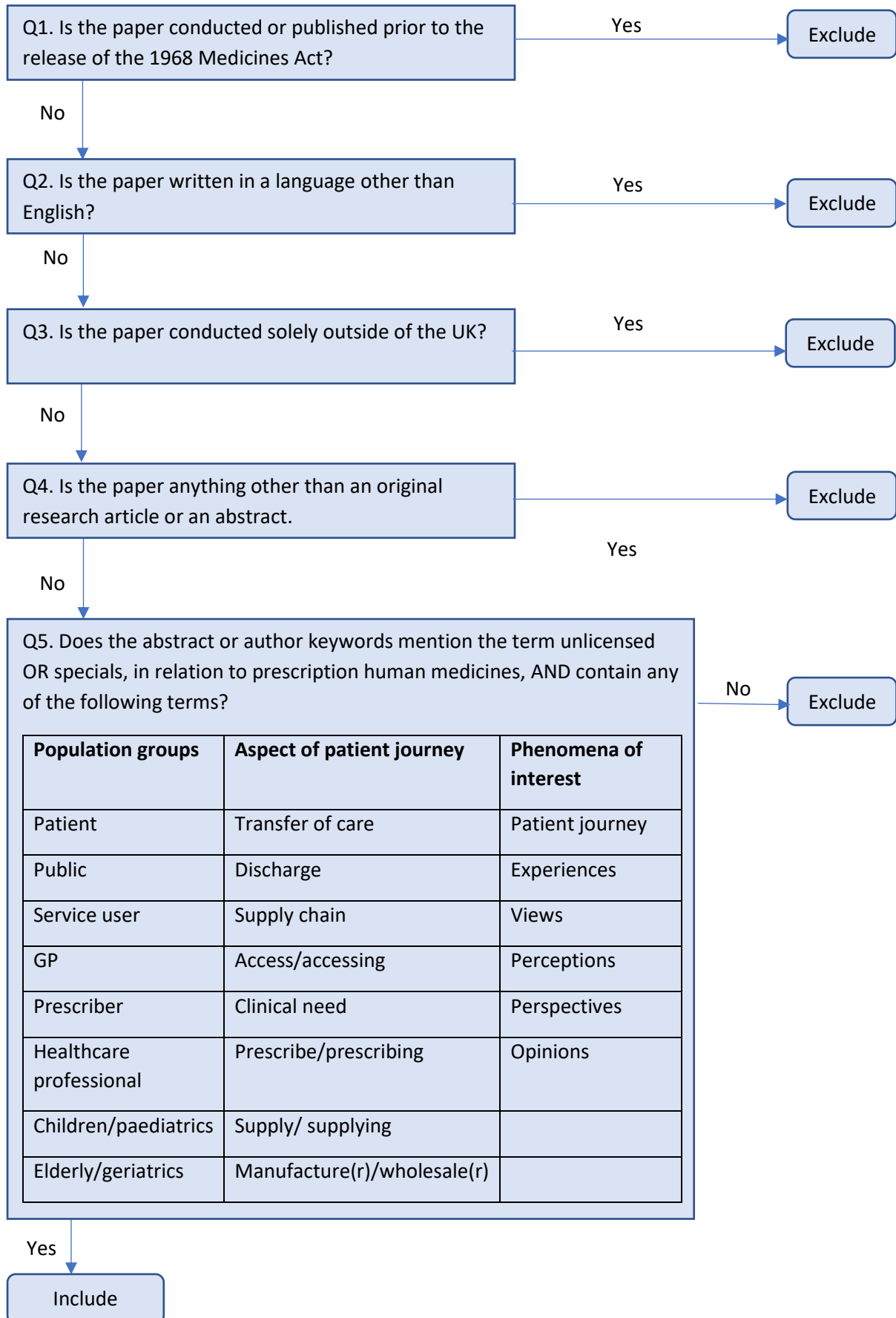
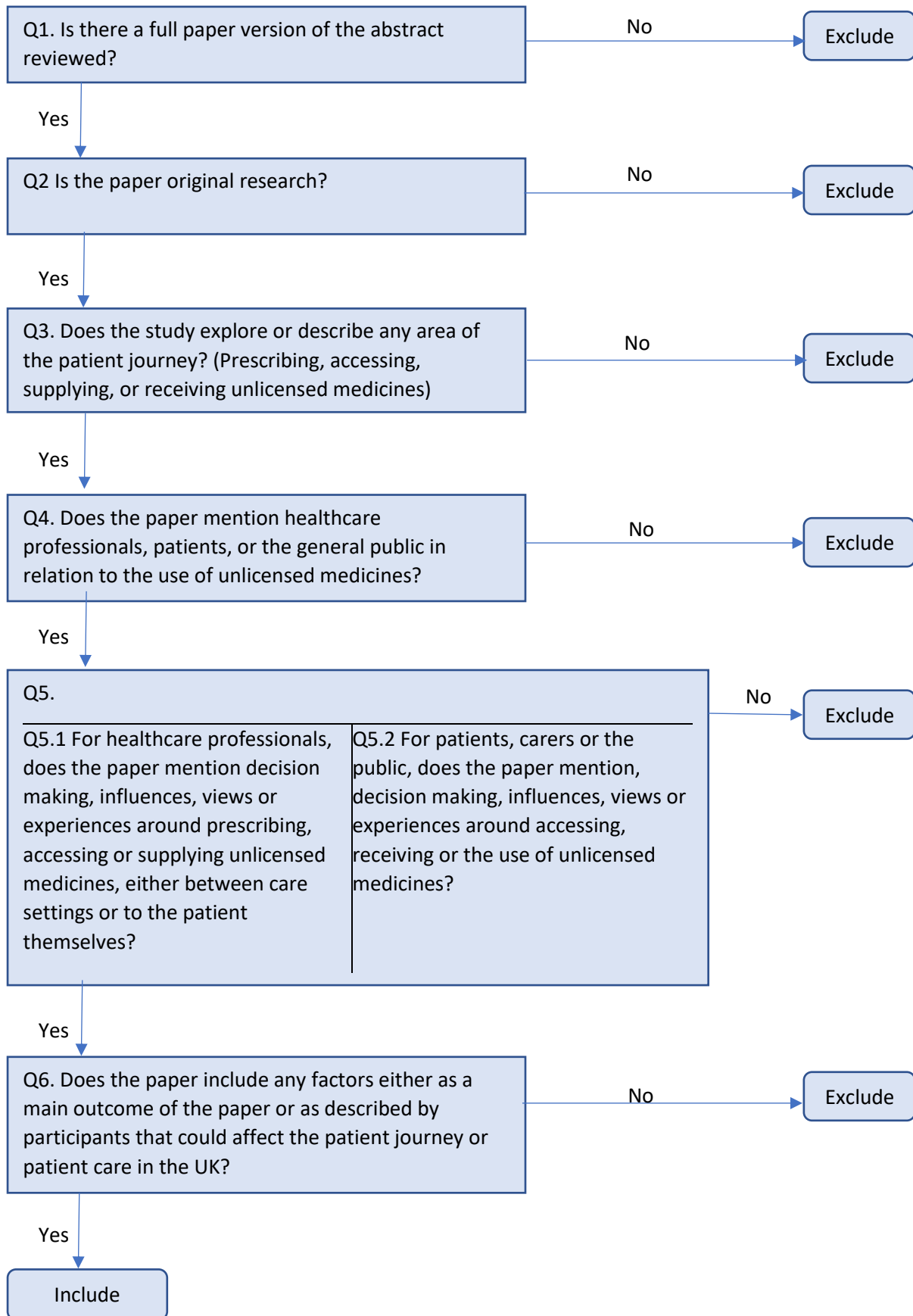


Figure 2.1 Screening criteria for abstracts included in systematic review

*Round-2* - Abstracts that were found to meet the screening criteria in round 1 were subsequently included in round 2, whereby the full texts were screened for inclusion using a second set of screening criteria (see figure 2.2). The approach for screening full texts can be seen below. As the researcher adopted a reflective approach, the screening criteria for round 2 was subject to change during the screening process to ensure all relevant studies were collected. This involved adding the final question to specify that the factor identified did not need to be the main outcome of the paper. The additional question was added when the researcher identified a record that contained useful information as a secondary outcome. As this was the first time the researcher encountered this, there was no need to re-screen those previously excluded, and screening continued using the additional question.

## Screening criteria for full text



**Figure 2.2** Screening criteria for full text inclusion in systematic review

### **2.3.5.3 Quality assurance**

Following the guidance laid out in the Cochrane handbook, the search strategy created was peer reviewed (Lefebvre *et al.*, 2020), in this case by the lead supervisor and the subject librarian. Multiple studies have found that the use of a second reviewer throughout the screening process can help to improve the transparency and reliability of the review results and reduce the likelihood of missing relevant studies (Edwards *et al.*, 2002; Waffenschmidt *et al.*, 2019). The systematic review approach of quality assurance was followed, and two reviewers were used to improve the transparency and replicability of the search strategy and screening criteria along with the consistency of the studies included in the review.

The researcher and the lead supervisor both took part in the deduplication process and the reflective approach of developing the screening criteria for abstracts. The researcher discussed multiple duplications with the lead supervisor, comparing the potential duplicates to discuss any differences found in the exports in Mendeley® and to determine which studies needed to be removed. The researcher and lead supervisor also reviewed and constructed the screening criteria together, this included running trials using the screening criteria with a few studies and having discussions about the effectiveness of the terms and questions used to successfully screen out irrelevant information.

To ensure the screening criteria were being applied consistently, a number of abstracts (approx. 25%) were selected to be reviewed with the lead supervisor. A comparison of the studies selected and any disagreements or inconsistencies about inclusion were discussed and resolved. Due to the broad inclusion criteria there were no disagreements when comparing selected studies, however where the researcher was unsure about whether a record should be included this was discussed with the supervisor and they decided upon together. The researcher continued to screen the remaining abstracts for inclusion using the same process as discussed and trialled with the supervisor.

### **2.3.6 Data collection process**

After the papers were screened for inclusion in round 2, descriptive information about each paper was collected. To extract and collect qualitative data, the researcher created a modified data extraction form, based on the JBI-QARI Data Extraction Form for Interpretive and Critical Research (Aromataris and Munn 2017) and the SURE checklist for identifying barriers and enablers to health systems (Ochodo *et al.*, 2017). These data extraction forms were selected as they had been used effectively in previous systematic reviews, and the researcher saw how valuable information could be gained from both methods of data extraction, and decided to create a combination of the two forms to specifically address the aims of this review. The modified form allowed the researcher to specifically look for findings

related to the patient journey and care when receiving an unlicensed medicine in the UK, and the factors, or enablers and barriers that have been reported to affect it across the healthcare system. An example of a completed version of the modified data extraction form for collecting information from qualitative studies can be seen in Appendix 2. For quantitative studies, any quantitative findings reported that would impact the patient journey or care related to the use of unlicensed medicines were recorded, and the researcher made notes on any barriers or enablers that were described within the research. The researcher read the papers in full, highlighting any findings or results that were perceived to have an impact on the patient journey or care, and extracted this information by completing the modified data extraction form or creating tables to record any relevant statistical findings.

#### **2.3.6.1 Data items collected from included studies**

More specifically, data items included descriptive information about the studies involved, such as date of publication, area within the UK, number of participants, participant population groups, study methods, unlicensed medicines used (if specified). From qualitative studies, data was considered to be any views or experiences given where the patient journey was affected, or could be affected, using quotations directly from the text to evidence findings, if possible. From quantitative studies, data related to the patient journey or care was collected for example, prevalence of unlicensed medicine use, number of admissions/errors/adverse drug reactions or if survey results of opinions or experiences related to the use of unlicensed medicines were reported as percentages.

#### **2.3.6.2 Outcome measures**

To address the aims of the review outcome measures included any factors that were reported or recorded to affect the patient journey or patient care, when receiving an unlicensed medicine in the UK.

#### **2.3.7 Risk of bias in individual studies**

Due to the variety of methods and designs to be included in the review, quantitative and qualitative studies were reviewed and appraised for quality using different checklists. Qualitative studies were reviewed for quality using the Critical Appraisal Skills Programme (CASP) qualitative studies critical appraisal checklist and quantitative studies were reviewed using the most suitable CASP checklist (cohort, case control) (CASP 2019). Scores for quality were provided for each study included in the review and the results of this are outlined in the results/discussion.



### 2.3.8 Data synthesis

As the studies included in the review contained high levels of heterogeneity in terms of designs and methods, a meta-analysis or meta-ethnography was not possible, and the evidence was synthesised using narrative synthesis. A narrative synthesis relies on using words and text to explain the findings of studies and aims to tell the 'story' of the evidence (Popay *et al.*, 2006). The researcher followed the guidance laid out by Popay *et al.*, which describes 4 key components to narrative synthesis, these are:

1. *Developing a theory of how the intervention works, why and for whom*
2. *Developing a preliminary synthesis of findings of included studies*
3. *Exploring relationships in the data*
4. *Assessing the robustness of the synthesis*

As the study did not aim to produce a theory the first component was not used. The remaining three elements involved describing the studies included, splitting or grouping the studies to synthesise separately, highlighting key areas of similarities or differences between the studies, and creating tables to compare results related to the research question (Ryan 2013). The aim of the review was to identify factors that impact the patient journey and care when receiving an unlicensed medicine, hence the results were split into the different stages of the patient journey or the different aspects that would be affected e.g., safety, before synthesis. This method allowed the researcher to review all available evidence and focus on the research questions and aims, and to identify factors that were seen to affect the different aspects of the patient journey or care when receiving an unlicensed medicine in the UK.

There are multiple variations in the methods used when narrative reviews are conducted, including content analysis, interpretive synthesis, framework synthesis and thematic synthesis (Snilstveit, Oliver and Vojtkova 2012). As well as using the modified data extraction form to gain information from the studies (see Appendix 2), the researcher chose to follow the stepwise approach of thematic synthesis presented by Lucas *et al* (2007), where after studies had been grouped into subgroups under questions derived from the aims of the review, study commentaries were created for each study before the themes were determined and before subgroup synthesis began. The study commentaries highlighted key aspects of the research findings in relation to the research question and the authors conclusions. The specific methods used were determined based on the final results gained and which method was decided to be most appropriate.

## 2.4 Results

The PRISMA flow chart containing the numbers of results gained at each stage of the study is presented in figure 2.3.

### 2.4.1 Study selection

After conducting the searches across all seven databases, a total of 2,129 documents were initially identified, exported and stored in Mendeley®. At the end of the deduplication process, a total of 1,264 documents were excluded leaving 865 to be reviewed in round 1.

#### 2.4.1.1 Round 1

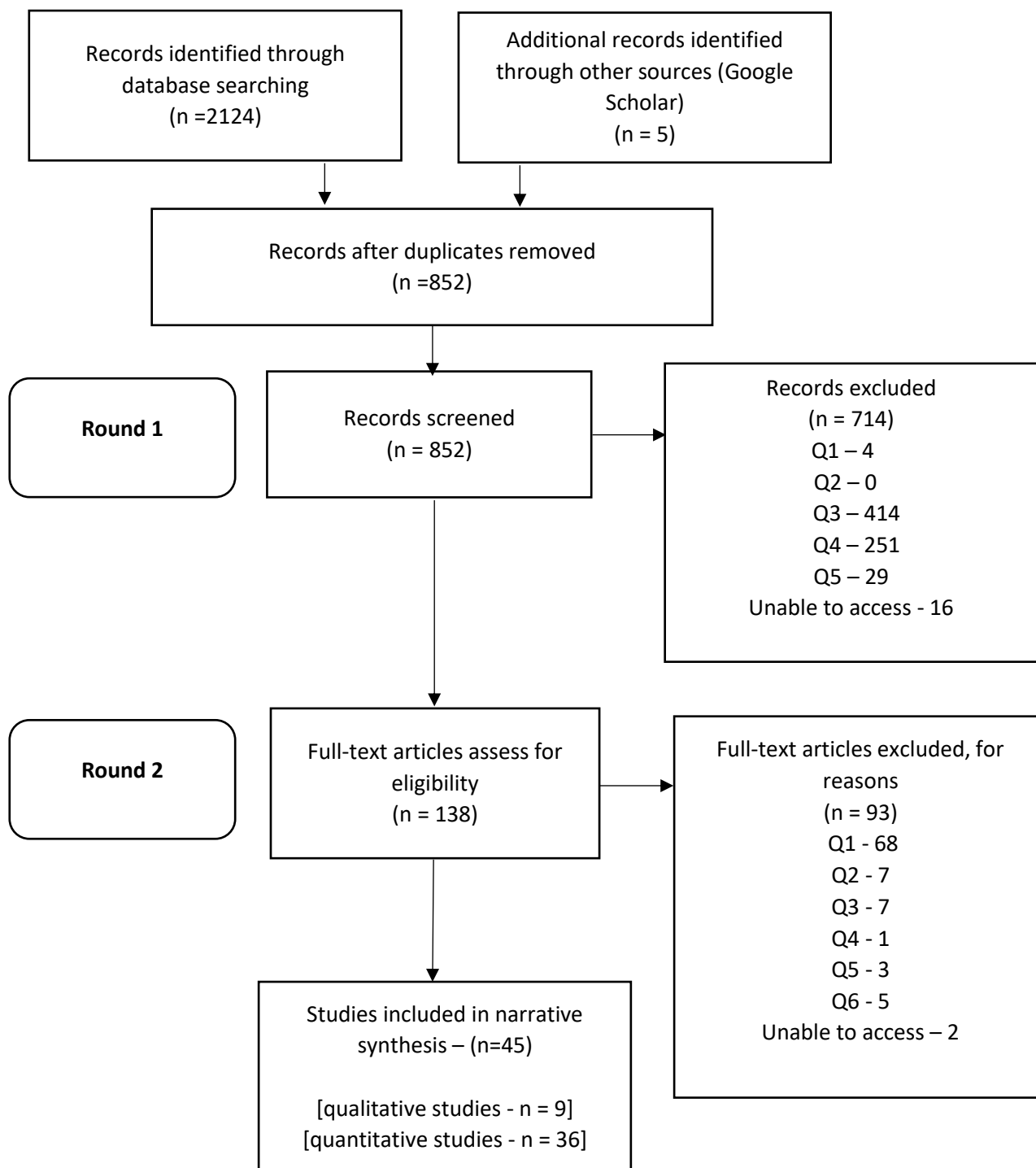
While screening the abstracts using the criteria (see 2.3.5) it became clear that Mendeley® had not successfully removed all of the duplicates in the sample and a further 13 documents were manually removed, leaving a total of 852 documents to be included in round 1. An example of this was a study entitled “Propylene Glycol Intake from Medications used on Paediatric Intensive Care”, this was recorded in Mendeley® under two different years 2013 and 2014, and with varying authors. After reviewing the different versions, it became clear that the study and results discussed were the same, however the study was published as an abstract for two different conferences and that Mendeley® had listed only some of the authors for one version and the remaining authors for the other. As a result, one copy was excluded from the sample. Another example of this issue was a news related article which had the same content but was recorded in Mendeley® under two slightly different titles, “Doctor who injected her sister with unlicensed drug is struck off register”, and “Doctor is struck off after injecting her sister with an unlicensed drug”. After reviewing both versions, it was clear the articles were the same and was written by the same author, but had been published on two different websites, resulting in one version being removed from the review.

The abstracts of the 852 remaining papers were screened for inclusion, of these 714 were excluded leaving 138 documents to reviewed in the second round of screening for full texts (see PRISMA flow chart). At this stage any relevant conference abstracts were included and moved on to round 2 in the hopes of accessing a full version of the study, whereas editorials and newsletters like the example given above were removed, as they were not original research. During the screening process, a number of abstracts could not be accessed online. To overcome this the researcher sought access to these abstracts using multiple methods. This included using the help of the subject librarian with more extensive access to journals or databases than the researcher, through the use of the University library loan service where hard copies in the library could be accessed by request and as a scanned version, or by contacting the authors directly to gain access to abstracts and full texts. This

process continued to be completed while round 2 began. Multiple documents were accessed successfully through the library loan service and one author responded to say that they were expecting to publish the full version of a conference abstract within the next six months, which meant the full version could not be accessed at the time of the review and as a result the abstract was screened out during round 2.

#### **2.4.1.2 Round 2**

The remaining 138 studies that resulted from screening abstracts for inclusion in round 1, were then reviewed using the screening criteria for full texts (see 2.3.5) which left a total of 45 studies to be included in the review.



**Figure 2.3** PRISMA flow diagram with number of studies excluded for each of the screening criteria questions (figure 2.1 and 2.2) and final number of studies included in the systematic review

## **2.4.2 Developing a preliminary synthesis**

The researcher followed the guidance laid out by Popay *et al* (2006), and the stepwise textual narrative synthesis as described by Lucas *et al* (2007). Preliminary synthesis involved using multiple tools and techniques such as producing a textual description of the studies involved and tabulating descriptive characteristics. This allowed the researcher to familiarise themselves with the data. Preliminary synthesis also involved grouping the studies into areas identified by the research as affecting the patient journey or care when receiving an unlicensed medicine in the UK.

### **2.4.2.1 Characteristics of studies included in the review**

A total of 45 studies were selected for the full review and narrative synthesis, table 2.3 outlines descriptive information about the characteristics of included studies. This includes the study number that will be used to refer to each study, the author and year the study was conducted, the study design, the age groups of the participants or cohort being explored, the sample size and the unlicensed medicine being studied (if the study specified this). A mix of designs were included in the review, with a range of focusses, consisting of 36 quantitative papers and 9 qualitative papers.

#### **2.4.2.1.1 Qualitative summary**

The 9 qualitative papers included in the review contained a range of methods and analytical techniques: two studies (26,33) conducted semi-structured interviews and used thematic analysis, a further 3 studies (11,15,28) used semi-structured interviews but with grounded theory, content analysis or framework analysis respectively. One study used structured interviews (27). Two studies conducted focus groups (8,20) and used thematic analysis and framework analysis respectively and the final study involved case reports (25). The samples used also varied between studies including a range of healthcare professionals (11,15,20,25,28,33), children (8) and carers of children/patients (25,26).

#### **2.4.2.1.2 Quantitative summary**

The 36 quantitative papers included in the review contained a range of designs and methods. There were a total of 12 prospective studies (4,5,7,19,24,34,35,36,37,40,42,43), 8 retrospective studies (9,16,21,23,32,38,39,44), 8 questionnaire/surveys (1,2,12,13,14,22,41,45), one Randomised Control Trial (RCT) (31), one crossover trial (6), one observational follow-up study (18), one nested case-control study (3), one exploratory study (17), one service evaluation (30), one study exploring the use of scaling methods for medicines (29) and one study exploring the release profile of certain medicines (10).

#### **2.4.2.1.3 Quality appraisal**

All studies were appraised for quality using a range of CASP checklists. For qualitative studies the qualitative CASP checklist was used and for quantitative studies other CASP checklists were used (RCT, cohort etc.). As CASP do not recommend using the checklist to score the studies, they were instead categorised as low, medium or high quality based on the number of questions on the checklist that were answered as yes, with medium having three or more 'can't tell' or 'no' responses and low quality having five or more answers that were not 'yes'. No studies were removed from the analysis due to a lack of quality. The quality appraisal results can also be seen in table 2.3 (results are presented by study type and then year order, starting with the most recent first). Examples of some completed checklists can be seen in Appendix 3.

**Table 2.3** Study characteristics and quality appraisal results of the 45 included studies in the systematic review by design type and recency of publication

Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
Qualitative studies						
33	Wale, Ireland and Yemm <i>et al</i> (2020)	Qualitative Semi-structured interviews	Adults	6 community pharmacy staff	N/A	High
26	Husain, Davies and Tomlin (2017)	Qualitative Semi-structured interviews	Paediatrics	15 parents and carers	Multiple	High
11	Donovan, Parkin and Brierley-Jones (2016)	Qualitative Semi-structured interviews	Unspecified	Healthcare professionals and patients	Multiple unlicensed medicines	Medium
25	Barrett, Broderick and Soulsby (2015)	Qualitative Case studies	Adults	2 patients	Unlicensed veterinary preparation of subcutaneous ivermectin	High
15	Haw, Stubbs and Dickens (2015)	Qualitative Semi-structured interviews	Adults	50 nurses	Not specified	High
20	Venables, Stirling and	Qualitative Focus groups	Adults	19 hcps	N/A	High

Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
	Batchelor <i>et al</i> (2015)					
8	Mukattash, Trew and Hawwa <i>et al</i> (2012)	Qualitative Focus groups	Paediatrics	123 pupils	N/A	High
28	Crowe, Tully and Cantrill (2009)	Qualitative Semi-structured interviews	Adults	47 healthcare professionals	N/A	High
27	Wong, Basra and Yeung <i>et al</i> (2006)	Qualitative Structured interviews	Paediatrics	216 carers	Not specified	High
Quantitative studies						
30	Bagshaw, McCormack and Brooks <i>et al</i> (2020)	Quantitative Service evaluation	Paediatrics	873 patients	propofol-remifentanil mixtures	High
18	Davis, Tipton and Sabir <i>et al</i> (2020)	Quantitative Observational follow-up study	Adults	26 patients	Recombinant vesicular 21stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV) vaccine as an unlicensed	High



Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
					emergency medicine	
9	Tiwari and Baldwin (2020)	Quantitative Retrospective study	Adults	177 patient referrals	Multiple unlicensed medicines	High
16	Weir and Paton (2020)	Quantitative Retrospective study	Paediatrics	7 adolescents	mepolizumab	Medium
32	Appleyard, Ashworth and Bedson <i>et al</i> (2019)	Quantitative Retrospective study	Adults	35031 Prescriptions	gabapentinoid	High
10	Chua, Richer and Swedrowska <i>et al</i> (2016)	Quantitative evaluation of medicines	N/A	7 products 2 UK unlicensed		High
21	Akram (2015)	Quantitative Retrospective study	Paediatrics	234 children	Multiple	High
17	McAuley, Hecht and Barnsdale <i>et al</i> (2015)	Quantitative Exploratory study	Not specified	36 drug related deaths	Unlicensed benzodiazepines	High
4	Bellis, Kirkham and Nunn <i>et al</i> (2014)	Quantitative Prospective study	Paediatrics	6020 patients	Multiple unlicensed medicines	High

Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
24	Lajoinie <i>et al</i> (2014)	Quantitative Prospective study	Paediatrics	908 dispensed medicines		High
3	Bellis, Kirkham and Thiessen <i>et al</i> (2013)	Quantitative Nested case control study	Paediatrics	1388 patients	Multiple unlicensed medicines	High
1	Notcutt (2013)	Quantitative Survey	Adults	124 patients	Sativex®	High
41	Bhoday, Conroy and Costa <i>et al</i> (2012)	Quantitative survey	Adults	40 members of Nottingham rps	Multiple	Medium
12	Chisholm (2012)	Quantitative survey	Adults	500 members of the public and 249 prescribing physicians	N/A	High
7	Conroy (2011)	Quantitative Prospective study	Paediatrics	158 reports	Multiple unlicensed medicines	High
13	Mukattash, Hawwa and Trew <i>et al</i> (2011)	Quantitative survey	Adults	1212 HCP	N/A	High
39	Ghosh, Arulrajan and Baldwin (2010)	Quantitative Retrospective study	Adults	114 patient notes	Multiple	High

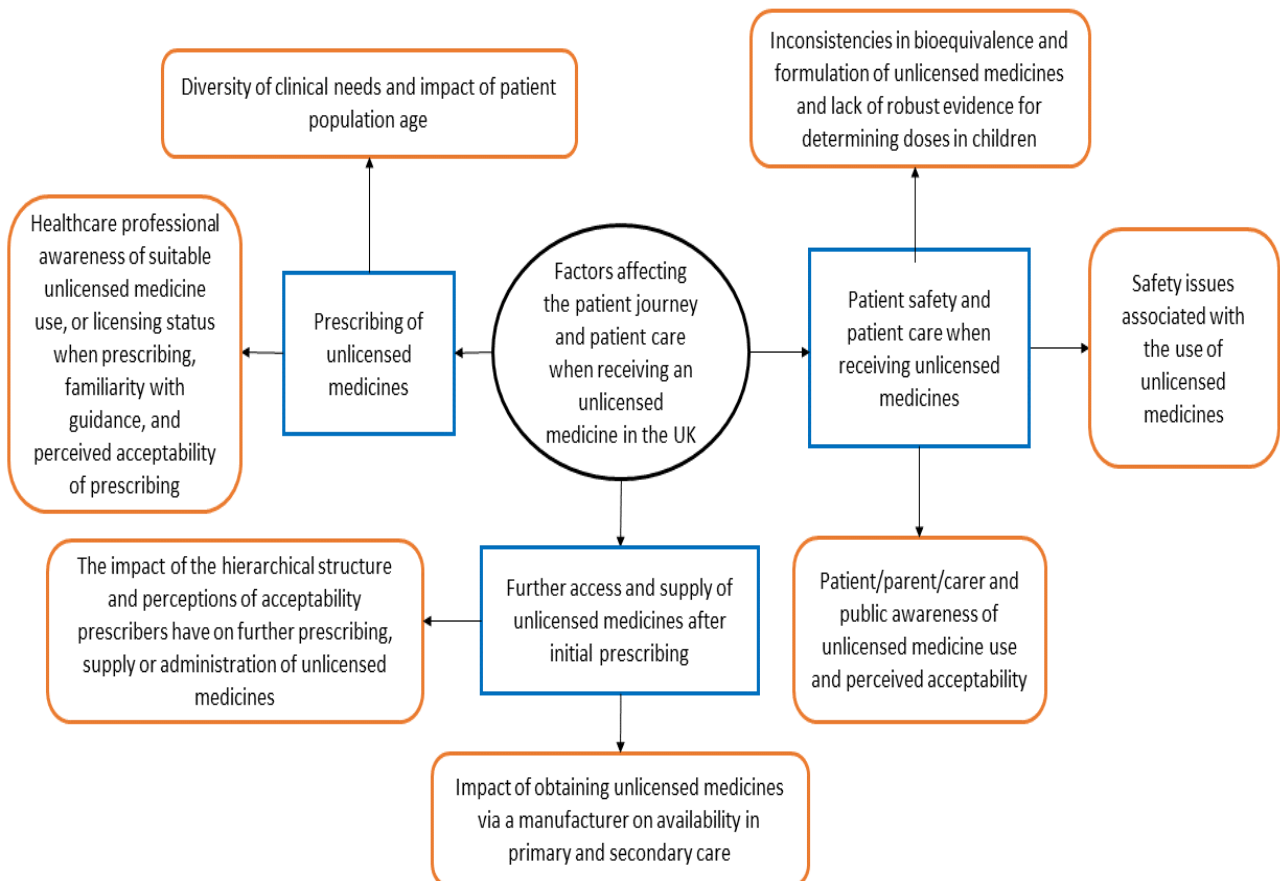
Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
6	Mulla, Hussain and Tanna <i>et al</i> (2010)	Quantitative Crossover trial	Adults	18 healthy adults	Unlicensed liquid captopril formulations	High
23	Viner, Hsia and Neubert <i>et al</i> (2009)	Quantitative Retrospective study	Paediatrics	1334 prescriptions for 452 patients	Antiobesity drugs	High
29	Johnson (2008)	Quantitative evaluation of medicines	Paediatrics	Unspecified?	Multiple	High
22	Mukattash, Millership and Collier <i>et al</i> (2008)	Quantitative survey	Adults	1000 participants	N/A	High
45	Mulla, Tofeig and Bu'lock <i>et al</i> (2007)	Quantitative survey	Adults	13 tertiary centres 13 hospitals	Unlicensed liquid captopril formulations	Medium
44	Helms, Daukes and Taylor <i>et al</i> (2005)	Quantitative Retrospective study	Paediatrics	214 medicines	None found off-label only	High
35	Conroy, Newman and Gudka (2003)	Quantitative Prospective study	Paediatrics	51 patients	Not specified	High
43	Dick, Keady and Mohamed <i>et al</i> (2003)	Quantitative Prospective study	Paediatrics	777 prescriptions 308 patients	Multiple	High

Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
31	Engelhardt, Steel and Johnston <i>et al</i> (2003)	Quantitative RCT	Paediatrics	60 patients	Tramadol	High
40	Shulman and Goldsmith (2003)	Quantitative Prospective study	Not specified	20 drug charts	Multiple	High
14	Wright (2002)	Quantitative survey	Adults	540 nurses	N/A	Medium
34	Conroy and Peden (2001)	Quantitative Prospective study	Paediatrics	715 prescriptions	Off-label no unlicensed	High
19	Johnson and Clark (2001)	Quantitative Prospective study	Paediatrics	478 prescriptions for 411 patients	Multiple	Medium
38	McIntyre, Conroy and Avery <i>et al</i> (2000)	Quantitative Retrospective study	Paediatrics	3347 prescriptions 1175 children	Multiple	High
42	Atkinson and Kirkham (1999)	Quantitative Prospective study	Not specified	76 patients 689 prescriptions	Multiple	High
36	Conroy, McIntyre and Choonara (1999)	Quantitative Prospective study	Paediatrics	455 prescriptions for 70 patients	Multiple	High

Study numbers	Author (year)	Study design/ Type of study	Age group	Sample size	Unlicensed medicines used (if specified)	Quality appraisal results (low/medium/high)
2	Howell and Madej (1999)	Quantitative Survey	Adults	169 clinicians	N/A	High
5	Turner, Nunn and Fielding <i>et al</i> (1999)	Quantitative Prospective study	Paediatrics	1046 admissions	Multiple unlicensed medicines	High
37	Turner, Longworth and Nunn <i>et al</i> (1998)	Quantitative Prospective study	Paediatrics	609 patients	Multiple	High

### 2.4.3 Thematic analysis

Reflexive thematic analysis (see 3.3.7) was conducted to determine different factors affecting the different areas of the patient journey and care when receiving an unlicensed medicine in the UK. Figure 2.4 presents an overview of the three themes constructed in respect to the area of the patient journey they relate to: (1) prescribing of unlicensed medicines; (2) further access and supply of unlicensed medicines after initial prescribing; and (3) patient safety and patient care when receiving unlicensed medicines. Some of the studies included in the review explored the views of multiple population groups or contained multiple factors that were seen to impact different areas of the patient journey. As such, these studies will be included in multiple themes across the patient journey however, different aspects of the results will be presented in relation to this.



**Figure 2.4** Themes and subthemes identified in systematic review exploring the factors affecting the patient journey and patient care when receiving unlicensed medicines in the UK

### **2.4.3.1 Theme 1- Prescribing of unlicensed medicines**

Numerous studies included in the review contained factors that were seen to impact the prescribing of unlicensed medicines. This included the diverse clinical needs of the patients and the awareness and acceptability around the use of unlicensed medicines among the healthcare professionals who prescribe medicines. The study commentaries are outlined below.

#### **2.4.3.1.1 Diversity of clinical needs and impact of patient population age**

A total of 19 studies included in the review described the use of unlicensed medicines (1,9,16,18,19,21,23,24,25,31,34,35,36,37,38,40,42,43,44). Reasons for this use included a lack of available or suitable licensed alternatives, when testing newer medicines, or when age had an impact on the need for unlicensed and off-label medicines.

The use of unlicensed and off-label medicines in specific care settings due to a lack of licensed alternatives was highlighted across many areas of care including intensive care. Shulman and Goldsmith (2003)(40) conducted a prospective study to assess the use of unlicensed medicines in an intensive care unit in a hospital in Middlesex. Drug charts were randomly selected over three weeks. A total of 20 drug charts were collected, with 18 including at least one unlicensed medicine. The 20 drug charts consisted of 176 medicines and 41% of these were unlicensed for the indication they were used, the route they were administered, or the dose used. All but two of the medicines were characterised as 'reasonable' by the authors, as there were no licensed alternatives, one contained a drug error, and the other was used off-label when a licensed medicine could have been used. Although only having a relatively small sample of drug charts from one hospital, therefore making the results not generalisable, the study highlights that unlicensed medicines are used commonly in intensive care units and usually for justified reasons such as a lack of licensed alternatives.

Unlicensed medicines were also reported to be used within palliative care. Atkinson and Kirkham (1999)(42) conducted a prospective study to explore the use of unlicensed medicines in a palliative care unit over four months. A total of 689 prescriptions consisting of 84 medicines were recorded. Unlicensed medicines were included in 15% of prescriptions. The authors described that most unlicensed medicine use was supported by evidence in the literature, however, one medicine was used unlicensed and without any supporting literature. Although the results were gained from a small 10-bed palliative care unit, the findings provide evidence of the need for the use of unlicensed medicines within palliative care.

The need for the use of a specific veterinary medicine used as unlicensed, due to the lack of a licensed alternative for human use, was reported by Barrett *et al* (2015)(25), who outlined

two case reports. The patients, a female aged 52 and a male aged 56, had severe *S. stercoralis* infection and were treated with an unlicensed veterinary medicine, subcutaneous ivermectin. Both patients improved after receiving the medicine, with improvements including a reduction in vomiting, ability to eat soft foods, and a reduction in confusion, and the female being discharged after 26 days. The authors acknowledged the limited amount of evidence available and despite the medicine being well tolerated in these cases, suggested further research would need to be conducted in order to determine safe dose ranges and toxicity levels. The results outline another clinical need for the use of a veterinary medicine as unlicensed, due to the lack of an available licensed alternative for humans.

Another example where the use of an unlicensed medicine was necessary to treat a specific case for which there were no other available treatments was reported by Davis *et al* (2019)(18). An observational follow up study was conducted with 26 participants who were injected with recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV) vaccine as an unlicensed medicine, after coming into contact with a healthcare professional who had been diagnosed with Ebola virus, as there were no licensed options at the time. The vaccine had been tested in several trials previously but had not received a license. Participants were aged between 24-67 years and were followed up 7 times periodically after vaccination, starting with a follow up after 30 mins and ending after 12 months. Although side-effects were experienced these were reported to be mild, including a fever and arthralgia, and the vaccine was tolerated, with none of the participants developing the virus. The results showcase the successful use of another unlicensed medicine when a specific clinical need arose, where the medicine had been tested in trials, but not yet received licensed status.

The use of unlicensed medicines was also reported to be clinically required when the licensed treatments available were not found to be effective for certain patients. Notcutt (2013)(1) conducted a short questionnaire with carers and patients receiving Sativex® as an unlicensed medicine to gain information about the effect of long-term use of the medicine on the function of patients. Sativex® had been involved in a number of RCTs but was unlicensed at the time the patients received it. A total of 124 participants were included in the questionnaire study, all of whom received this medicine as they were suffering from long-term diseases and had responded poorly to the previous treatment with licensed products for Multiple Sclerosis (MS). Participants described benefits to their daily living and abilities as a result of using Sativex®, with 94% of patients believing they had benefitted from receiving it as an unlicensed medicine. The authors recognised the limitations of their method such as a survey response rate of 57% that limited the ability to analyse for statistical significance, but



the sample was still relatively large and the findings highlight the clinical need of using unlicensed medicines when other licensed treatments are not effective.

Unlicensed medicines are also used to create alternatives from medicines licensed for other populations, and during new medicine testing. Tramadol is a medicine not licensed for paediatric use in the UK. Engelhardt *et al* (2003)(31) conducted a prospective, double blind RCT in children to compare the use of tramadol and morphine in a children's hospital in Scotland. A total of 60 participants were separated into three groups, one receiving morphine and two receiving different doses of tramadol. Morphine was associated with higher rates of vomiting compared to the tramadol groups. The results showed tramadol to have similar properties to morphine, with fewer side-effects, and the authors suggested it could be useful in paediatric anaesthesia if licensed for children. Although the samples were relatively small, the findings show the importance for trialling medicines that are licensed for adult populations as unlicensed medicines for children, in order to test for effectiveness and safety and hence ultimately improving current treatment methods.

Another study discussing use of unlicensed medicines for specific age cohorts and for a specific clinical need was conducted by Tiwari and Baldwin (2020)(9), who completed a retrospective study of clinical characteristics and treatments over five years, for patients referred to a specialist service, to explore the factors associated with the use of unlicensed medicines in patients with affective disorders. Patients were split into three clusters based on their diagnosis: unipolar depressive disorders, bipolar disorder and anxiety related disorders. One hundred and forty eight patients were assigned into the three clusters. It was found that unlicensed medicines were prescribed commonly across all groups, in a total of 74 patients (around 50%). The use of unlicensed medicines was not associated with diagnosis cluster, sex or physical co-morbidity. However, age was identified as a factor associated with their use, with 53% of patients under 65 being recommended unlicensed medicines, and only 28% of those aged over 65. The authors addressed their limitations, with the study successfully showing the extent of prescribing unlicensed medicines for affective disorders in tertiary care and the impact of age in this prescribing practice.

Many of the studies included in the systematic review conducted as part of this PhD, focussed on the use of unlicensed and off-label medicines for children across care settings, or as treatment for a range of specific conditions. Turner *et al* (1998)(37) conducted a prospective study over 13 weeks of medicines administered in a children's hospital in Liverpool, to explore the use of unlicensed and off-label medicines. In total, 2,013 medicines were provided to patients aged four days to 20 years, of which 25% were for unlicensed or off-label indications. This included the use of unlicensed 'special' medicines, the import of

medicines licensed in other countries and the off-label use of medicines for differing doses, routes of administration or for children outside the age range of the license. Thirty-six per cent of patients received one or more unlicensed or off-label medicine. The authors provided lists of the most commonly used unlicensed and off-label medicines and highlighted that, although both were used commonly, off-label medicines were more frequently prescribed than unlicensed medicines. Although the study was only conducted in one hospital over 13 weeks, the results provide valuable evidence on the uses of unlicensed and off-label medicines in children in a hospital setting.

The use of unlicensed and off-label medicines in children was also explored within primary care settings. McIntyre *et al* (2000)(38) conducted a retrospective analysis of prescriptions from one general practice in the Midlands for one year, exploring prescribing of unlicensed and off-label medicines in children aged 12 and younger. In total, 3,347 prescriptions were recorded in 1997, of which 0.3% were for unlicensed medicines and 10.5% were for off-label medicines. The most common use of off-label medicines was for differing doses compared to the doses licensed for children, with some medicine recommendations suggesting similar doses for newborns as for 10-year-olds, resulting in prescribers needing to go off-label to adjust doses for different ages. A total of 677 prescriptions for antibacterial medicines were recorded, 16% of which were unlicensed, and similar levels were seen for off-label medicines. The results highlighted the use of off-label medicines in specific patient populations in general practice. Although the study was conducted over 20 years ago, the findings show that unlicensed and off-label medicines have been used in primary care in children for some time and highlight increased rates for specific clinical needs, such as for antibacterial indications.

The more frequent use of off-label medicines compared to unlicensed medicines in primary care for children was also reported by Helms *et al* (2005)(44), who assessed prescribing data over one year from the General Practice Administration System for Scotland. The study investigated a total of 214 medicines and the results indicated no prescriptions for unlicensed medicines but showed that off-label medicines were prescribed commonly for 0-16-year-olds, in 20-35% of overall prescriptions, across the ages. Multiple reasons were provided for the off-label use of medicines, with the most common being lower doses than recommended on the licence for children, followed by higher doses than recommended, lower ages than recommended and unlicensed formulations of licensed medicines. Although the study only took place over one year, the results provided an insight into the reasons many children are prescribed off-label medicines, and highlight the limited range of licensed medicines suitable for children.

When exploring the use of unlicensed medicines in children, numerous studies reported varying rates for different therapeutic areas. Akram (2014)(21) conducted a retrospective analysis of discharge summary letters over 15 years to explore the use of psychotropic medications from a psychiatric ward for children. Of the 117 prescribed psychotropic medicines analysed, 50% were for unlicensed or off-label medicines, with the most common being risperidone. Unlicensed or off-label medicines were most commonly used for sleep disturbances and tics. The study was longitudinal and gathered information over a long time period, increasing the validity of the findings. The results highlight the high use of unlicensed and off-label medicines in the children's psychiatric ward and provided some information on the conditions these are most regularly used for.

Multiple reasons for needing to use unlicensed or off-label medicines in children were also outlined by Johnson and Clark (2001)(19), who conducted a prospective study over 6 months, collecting information about new prescriptions from 21 child and adolescent mental health services. Out of 478 new prescriptions, 2% were for unlicensed medicines and 39% were for off-label medicines. The unlicensed medicines were used for sleep disturbances and the off-label medicines were used for numerous reasons, including use for different age groups than licensed, use for a different indication, or used at differing doses. Although the study was only conducted over six months, the findings highlight the small number of unlicensed medicines prescribed and give some insight into the ways licensed medicines are used off-label in child and adolescent mental health services.

The use of unlicensed medicines for children was also highlighted within gastroenterology. Dick *et al* (2003)(43) assessed the use of unlicensed and off-label medicines in children who were prescribed medicines from a gastroenterology unit and discharged to the community, and explored how much information was available about these medicines in the British formularies. Prescriptions from 3 gastroenterologists over a 6-month period were collected, and the authors identified 308 patients who had received 777 prescriptions. Of these, 49% were for unlicensed or off-label medicines; 291 medicines were prescribed off-label and 93 were unlicensed. The authors found that only the 'Medicines for Children' formulary contained information on more than half of the commonly prescribed off-label or unlicensed medicines, with other formularies lacking information for many paediatric doses. The findings help to show the ongoing use of unlicensed and off-label medicines within paediatric gastroenterology and show how many British formularies lack information for medicines commonly prescribed in children, highlighting a lack of prescribing guidance in this area.

In a different study, off-label medicines were highlighted for use within pain management for children. Conroy and Peden (2001)(34) conducted a prospective study to explore the use of

unlicensed and off-label analgesic agents used to manage pain in children. Data was collected over 4 weeks, from two wards in a children's hospital in Derbyshire. A total of 715 prescriptions were analysed, 67% of which were for licensed medicines and 33% for off-label. No unlicensed medicines were recorded. Off-label medicines were used due to the patients' age or weight when medicines were not licensed for children, or because the patients required differing doses, routes or indications than the recommendations provided for medicines licensed for children. Although the study was conducted at one hospital for a relatively short time, the results show that around a third of the medicines prescribed can be for off-label medicines for treating children, as the licensed recommendations are often not suitable for this age group.

The use of unlicensed medicines for treating obesity in children was reported to have increased over time. Viner *et al* (2009)(23) explored the use of unlicensed medicines for obesity in children aged 0-18 in the UK, specifically the use of orlistat, sibutramine and rimonabant. This was achieved by accessing population-based information from the UK General Practice Research Database, collected over seven years. The study found that 452 patients received 1,334 prescriptions, and that anti-obesity prescribing had increased by 15 times between 1999-2006. Female patients were more likely to be prescribed anti-obesity medicines (82.3%). No children below the age of 10 were prescribed the anti-obesity medicines. Orlistat was the most commonly prescribed medicine at 78.4% of prescriptions, with only one participant having been prescribed rimonabant. The results came from a national data collection database over a long period of time, increasing the validity of the findings, and highlight the increasing use of unlicensed anti-obesity medicines to treat children and adolescents.

One study highlighted the use of unlicensed and off-label medicines in the treatment of leukaemia in children. Conroy, Newman and Gudka (2003)(35) conducted a prospective study to explore the use of unlicensed and off-label prescribing in children with acute lymphoblastic leukaemia and other malignancies. Prescriptions were collected over four weeks from Queen's Medical Centre in Nottingham. Fifty-one patients received a total of 569 prescriptions. Of these, 55% were for licensed medicines, whereas unlicensed medicines accounted for 19% and off-label medicines made up 26% of prescriptions. A key finding in relation to the prescribed unlicensed medicines was that they accounted for 40% of overall cytotoxic agent prescribing as there were no licensed alternatives for use within this age group. The results show that many medicines used to treat paediatric leukaemia are not licensed specifically for children, highlighting another therapeutic area where the clinical need arises for the use of unlicensed medicines in this specific patient population.

The need for the use of unlicensed medicines in children was not just highlighted due to a lack of licensed medicines available but also when the licensed medicine was found not to be suitable for the specific patient, such as when allergies are present or when the licensed medicine has led to treatment failure. Weir and Paton (2020)(16), conducted a retrospective study exploring the unlicensed use of mepolizumab in adolescents with eosinophilic asthma. A total of seven participants aged between 11-17 years were included in the study, of whom three had already tried omalizumab (a licensed alternative), which resulted in either treatment failure or allergic reactions. An adult dose of mepolizumab was given to participants monthly for 12 months and outcomes were reviewed after the 4<sup>th</sup> and 12<sup>th</sup> doses. Asthma attacks were reported to decrease significantly during treatment with mepolizumab with a reduction in hospital visits required compared to the 12 months prior to receiving treatment, however lung function was not improved across all patients. Although the sample size was very small, the findings show a significant improvement for adolescents who were unable to receive the licensed formulation due to treatment failure and allergies, and highlight another important area for the use of unlicensed medicines, as alternatives when the licensed options are not suitable to meet the clinical needs of the patients.

Specific age ranges within paediatrics were also highlighted as using higher numbers of unlicensed and off-label medicines. Conroy, McIntyre and Choonara (1999)(36) conducted a prospective study of prescriptions from a neonatal intensive care unit over 13 weeks. A total of 455 prescriptions were recorded for 70 babies aged 26 to 36 weeks with 90% of patients being prescribed at least one medicine that was unlicensed or off-label. Unlicensed medicines accounted for 45 prescriptions and off-label medicines accounted for 249 prescriptions. The unlicensed medicines were categorised into the different types used, such as specials, modifications to licensed medicines, and new medicines. Off-label medicines were categorised into reasons for use such as outside of the doses recommended, outside of licensed age range and used for non-licensed indication. The results demonstrate an extremely high use of unlicensed and off-label medicines in treating neonates and the lack of available licensed medicines for this sub-group of children.

As detailed above, high use of unlicensed and off-label medicines is noted among younger children more generally, not only neonates. When looking at a different age group of young children, one study specifically explored the suitability of their use as opposed to licensed liquid or solid alternatives. Lajoinie *et al* (2014)(24) conducted a prospective study over one week, which aimed to assess the cost saving potential of switching oral liquid medicines with solid forms for children aged over two years. Of the 476 liquid formulations included in the study, 92% were available as a marketed solid form, with only 13% of the dispensed liquid formulations not corresponding to a licensed alternative. If the liquid medicines were to be

substituted to the licensed solid form medicines, the potential savings were estimated to be between £238,000 to £410,000 annually for one site. The authors acknowledge that this may not be practical in all situations as some children may have difficulties swallowing solid medicines and may truly require the use of unlicensed liquid medicines.

### **Summary of subtheme**

The papers discussed above describe a range of clinical circumstances that justify the use of an unlicensed medicine, such as specific allergies to licensed medicines, treatment failure with licensed medicines, a lack of licensed medicines available to treat the condition or a lack of suitable licensed medicines for specific patient populations, notably children. The rates at which unlicensed medicines were used in children differed between studies, with neonates being reported to receive the highest number of unlicensed or off-label medicines.

#### **2.4.3.1.2 Healthcare professional awareness of suitable unlicensed medicine use, or licensing status when prescribing, familiarity with guidance, and perceived acceptability of prescribing**

A total of five studies included in the review described different aspects of healthcare professional awareness, including awareness of the licensing status when prescribing unlicensed medicines, awareness of suitable uses for unlicensed medicines or guidance available to them. The studies also described the acceptability of prescribers when prescribing unlicensed medicines and discussed how this could impact prescribing practices (2,11,12,27,28).

Howell and Madej (1999)(2) used a computer assisted audience response system to ask questions to members attending the 1997 Obstetric Anaesthetists' Association (OAA) annual meeting, about the use of unlicensed medicines. Participants included 169 obstetric anaesthetists. The responses highlighted that, although the majority were aware of the use of unlicensed medicines in practice and had experience prescribing them, there was a lack of understanding about some of the indications for which drugs were originally licensed for and an associated lack of appreciation for the potential side-effects. Around 40% of participants reported using the unlicensed medicine propofol in pregnancy, although the authors highlight propofol was specifically stated not to be used during pregnancy by the manufacturer. Almost 80% of participants believed that the OAA should issue guidance on drug practice and poll members for information on their current medicine uses. Eight participants had been involved in court cases as a result of the use of unlicensed medicines, two of whom did not specify the outcome of the cases, two who had successfully defended their use of the medicine, whereas for the remaining four the use of the unlicensed medicines was criticised by the court. Although the participants were given limited time to

respond to the questions, which could have introduced bias or inaccuracies in the responses, the results provide evidence towards how experiences of specialist clinicians around the use of unlicensed medicines and awareness of guidelines, or lack thereof, can directly impact prescribing practice.

When looking at the views and experiences of healthcare professionals, Donovan *et al* (2016)(11), aimed to explore the use of unlicensed medicines across primary and secondary care, by conducting semi-structured interviews with prescribers, pharmacists, and patients. Preliminary themes identified included a lack of information and training for healthcare professionals, which impacted awareness around the use of unlicensed medicines. Prescribers reported that they were not always aware when they were prescribing unlicensed medicines. A full report was available, and this was included in the review. Although the full report alluded to some important factors from the perspectives of those involved, the reported methods and results did not provide enough detail for a qualitative study and after contacting the author, it was understood that a paper focussing on just the qualitative side of the study had yet to be published. However, the finding that some prescribers may not be aware when they prescribe unlicensed medicines highlights the importance of increasing awareness of the nature of unlicensed medicines among practitioners and adds a valuable finding to the review.

Prescribers' views around the use of unlicensed medicines and specific concerns held were highlighted by Chisholm (2012)(12), who distributed a questionnaire to explore the attitudes of 249 prescribers and 500 members of the general public. Only 14% of prescribers were very familiar with the guidelines on the use of unlicensed medicines and 17% felt comfortable to prescribe unlicensed medicines when licensed alternatives were available. The authors also found that 43% of prescribers viewed cost as the least important factor when deciding to prescribe unlicensed medicines, with safety and efficacy being ranked highest for prescribers. A total of 31% of prescribers reported they would not feel comfortable prescribing off-label medicines, however the confidence felt was higher in secondary care prescribers when compared to those in primary care. Most prescribers also reported concerns around their legal responsibility (76%) and concerns around safety and monitoring of patients receiving unlicensed medicines (71%). The study involved an adequate sample of participants and outlined the results clearly, providing valuable results and insights into the views of prescribers. The lack of familiarity with the guidance available, and the varying levels of confidence reported by prescribers across care settings along with the specific concerns outlined above, could all impact prescribing decisions.

The limited perceived experience of prescribers when using unlicensed medicines and the concerns they held were also seen to directly impact perceptions of acceptability and prescribing practice in a different study. Wong *et al* (2006)(27), conducted structured telephone interviews with parents of children who had recently been discharged from a hospital in London, to explore the availability of unlicensed or off-label medicines. Interviews were also conducted with 15 of the GPs who were responsible for the care of the discharged children. A total of 216 carers took part in the telephone interviews and it was found that 33% of them had difficulties accessing their medicines in primary care, with 26 participants describing GPs being unwilling to continue prescriptions for unlicensed medicines that had been initiated in secondary care. The GPs interviewed provided information on which unlicensed medicines they had decided not to prescribe and gave reasons for this. This included the medicine being too costly, being outside the prescribing guidance, a lack of experience or information and concerns about the additional responsibilities associated with prescribing unlicensed or off-label. The authors acknowledged that the children's hospital involved in the study typically dealt with complex cases so the results may not be generalisable. Nevertheless, the study highlights how the perceived limited experience of GPs on the use of unlicensed medicines directly impacted prescribing behaviours. Multiple other factors reported to impact GP prescribing behaviours were outlined by Crowe, Tully and Cantrill (2009)(28). Semi-structured interviews were conducted with 47 healthcare professionals working in a range of primary care roles in the North-West of England, to explore the factors that influence GP prescribing of specialist drugs. Framework analysis revealed six factors that included: the specific specialist medicine; the level of information they received from secondary care; the work involved and resources needed for shared care arrangements; the cost of the medicines; patient convenience, such as the ways the patient would need to access their medicines; their own areas of interest and knowledge along with discussion had with peers in the practice. The results help to highlight the views of primary care staff and identify a range of factors that influence the decision-making process when prescribing specialist drugs.

### **Summary of subtheme**

Overall, the awareness of suitable unlicensed medicine use, or licensing status when prescribing, familiarity with guidance, and perceived acceptability of prescribers across care settings were seen to directly impact the prescribing of unlicensed medicines. Specific factors were highlighted that impacted prescribers' decisions to prescribe, such as their own knowledge and experience, with some prescribers reporting they may not be aware of the licensing status when they prescribe unlicensed medicines, and higher levels of confidence being reported by secondary care prescribers compared to primary care prescribers. The



cost of the medicine and concerns over their legal responsibilities were also reported to impact on a GP's decision on whether to continue prescriptions for unlicensed medicines.

#### **2.4.3.2 Theme 2 – Further access and supply of unlicensed medicines after initial prescribing**

Two main factors were seen to impact healthcare professionals when continuing to prescribe previously initiated unlicensed medicines across care settings, or when accessing, supplying, or administering unlicensed medicines. The first factor was how the hierarchical structure within the healthcare system and the individual perceptions of acceptability impacted if and how unlicensed medicines were prescribed, supplied or administered. The second factor was related to the issues faced with accessibility when obtaining unlicensed medicines from suppliers.

##### **2.4.3.2.1 The impact of the hierarchical structure and perceptions of acceptability prescribers have on further prescribing, supply or administration of unlicensed medicines**

A total of four studies provided evidence about how the hierarchical structure of the chain of prescribing and the familiarity with, and acceptability of the use of unlicensed medicines among the healthcare professionals involved at different levels, was seen to impact the ability of pharmacists to obtain and supply unlicensed medicines or to impact the way unlicensed medicines are administered (14,15,33,41).

Wale *et al* (2020)(33) conducted semi-structured interviews with community pharmacy staff members in South Wales to explore their views and experiences around accessing and supplying unlicensed 'special' medicines. Six participants took part in an interview. Community pharmacy staff reported that they were not routinely receiving adequate information on the intended use and indication of the unlicensed medications, and in certain cases would contact the original prescriber to confirm whether the medication was clinically appropriate, before agreeing to proceed with supplying it. The concerns they had were alleviated by accepting the expertise of the original prescriber, showing how this perceived hierarchy had helped to increase the acceptability of community pharmacy staff in supplying unlicensed medicines. Participants also described issues with continuity, with GPs accidentally selecting an unlicensed product in their prescribing software, or deciding not to prescribe unlicensed medicines when requested to continue prescriptions originally initiated in secondary care. This lack of acceptability subsequently prevented pharmacy staff from being able to supply the medicine to the patients. Although the study only included participants from one small chain of community pharmacies the results give the first insight into the views and experiences of community pharmacy staff specifically in Wales. The study highlights how the acceptability of GPs around prescribing unlicensed medicines can impact

pharmacists' ability to supply unlicensed medicines, and how community pharmacist acceptability was impacted by the perceived expertise of the original prescriber.

The impact of GPs' acceptability when prescribing unlicensed medicine on the ability of pharmacists to supply unlicensed medicines was also reported by Conroy *et al* (2020)(41). An online questionnaire was distributed to members of the Nottinghamshire and Derbyshire Local Practice Forum of the RPS to explore the experiences of pharmacists when supplying unlicensed medicines to children. Of the 40 responses, seven participants reported issues that were experienced with GPs not being familiar with the use of the unlicensed medicine requested, requiring further information, being unwilling to prescribe, or prescribing with errors, or even the unlicensed medicines required not being listed on the GP computer system. All these factors contributed to delays before patients could be supplied with their medicine. The findings highlight the ongoing issues faced by pharmacists when supplying unlicensed medicines and provide evidence of how other healthcare professionals' perceptions of acceptability around prescribing these medicines can disrupt pharmacists' ability to supply unlicensed medicines and lead to delays in treatment.

The prescribers' views and perceptions of acceptability around the use of unlicensed medicines were also reported to impact the way unlicensed medicines were administered to patients. In 2002 Wright (14) distributed questionnaires to nurses working in independent nursing homes, with a total of 540 out of 763 questionnaires returned. The results showed that around 15% of residents had difficulties with swallowing medicines, which resulted in them spitting it out or hiding the medication. The unlicensed crushing or opening of medicines was reported by nurses to happen weekly in 80% of the nursing homes whose nurses responded to the survey, with 58% of participants suggesting that the prescriber may suggest the crushing of tablets. One of the reasons this was perceived to be preferable to prescribing unlicensed liquid medicines was the associated high cost involved should unlicensed prescribing take place. The findings highlight key experiences of nurses in nursing homes who, even though not directly involved in the decision-making process to prescribe an unlicensed medicine, are still in some way legally responsible for the medicines they administer to patients, and the impact of prescriber attitudes on how unlicensed medicines are supplied and administered to patients.

The influence of prescribers' perceptions of acceptability of which medicines are supplied or how they are administered was also supported by Haw, Stubbs and Dickens (2015)(15), who explored the awareness and views of mental health nurses around medicines management. A total of 50 nurses working at a secure psychiatric hospital were included in the study. Clinical vignettes were provided to participants, with dilemmas to discuss during semi-

structured interviews. The nurses' perceptions were reported to impact practice with only 20% of participants reporting that they would administer unlicensed medicines if they had no knowledge of their use, and most participants suggested they would want to know side effects and potential benefits. When discussing off-label medicine prescribing with no clear evidence of benefits, 52% said they would not administer the medicine. However, 8% of nurses suggested they would still provide it rather than challenge the prescribing doctor, highlighting the influence of the prescribing doctor on the administration of unlicensed medicines and reinforcing the impact of the hierarchical structure, as reported previously by pharmacists. The study clearly identified factors that influence mental health nurses' decision-making when administering unlicensed or off-label medicines. The authors recognised that as participants were working in specialist settings, the results may not be generalisable. However, the results are valuable in better understanding the views and experiences of mental health nurses, and how individual perceptions across the supply chain can impact the administration of unlicensed medicines.

### **Summary of subtheme**

Overall, the perceptions of healthcare professionals were seen to impact the further prescribing, access, supply and administration of unlicensed and off-label medicines. GPs' acceptability of the use of unlicensed medicines led to decisions not to prescribe, which disrupted the supply chain and halted the community pharmacy staffs' ability to supply unlicensed medicines to patients. Community pharmacy staff and nurses expressed that accepting the expertise of the original prescriber helped to reduce their initial concerns or perceived limited experience. The hierarchical structure within the healthcare supply chain and the perceived trust or reliance of community pharmacy staff and nurses on the original prescribers' perceived knowledge or expertise, in some cases was seen to lead to reluctance to question the prescriber and other times to accepting the prescribed item without being satisfied that it is clinically appropriate, directly impacting the supply and administration of unlicensed medicines.

#### **2.4.3.2.2 Impact of obtaining unlicensed medicines via a manufacturer on availability in primary and secondary care**

A total of three studies included in the review highlighted issues with the accessibility and availability of unlicensed medicines via an unlicensed medicines manufacturer (20,27,33). This included difficulties for pharmacists across care settings to find manufacturers to source the medicine.

Specific issues related to the accessibility and availability of unlicensed medicines were reported by Venables *et al* (2015)(20), who conducted focus groups with nurses, medical

practitioners and pharmacists to explore the problems faced with licensed and unlicensed oral medicines used for children. Nineteen participants in total took part in the study from two children's hospitals in England. All participants discussed issues around the use of a specific liquid unlicensed special medicine, omeprazole, reporting difficulties around costing, obtaining and storing the medicine and short expiry dates. It was found that pharmacists had increased knowledge and understanding of the use of specials compared to the other HCPs. Pharmacists reported further problems associated with the use of this medicine, such as the varying bioequivalence of the formulations received, depending on the manufacturer. The results show that when discussing issues around children's medicines, the use of 'specials' was raised by all participants with pharmacists, further highlighting some of the key issues they perceived to be associated with accessing and supplying unlicensed medicines to patients.

Issues experienced by pharmacists around the accessibility of unlicensed 'special' medicines were also reported by Wale *et al* (2020)(33) (study described in subtheme 2.4.3.2.). Community pharmacy staff reported numerous examples of not being able to access the specific unlicensed medicine required from their regular supplier, having to find other suppliers to source the medicine. In one occasion a manufacturer could not be identified at all. These challenges with accessibility led to longer lead times, treatment delays, and in one case treatment disruption where the patient was referred back to secondary care, but hospital staff could not access the unlicensed medicine from their manufacturers either. Issues with the availability of specific formulations of unlicensed products were also reported, with examples including certain suppliers only having a gel available when a cream was originally prescribed. Although the study only included participants from one small chain of community pharmacies, the results highlight that even when the clinical need for an unlicensed product has been established, issues with the inconsistent accessibility of the appropriate medicine from manufacturers may impact pharmacists' ability to supply the medicine in a timely manner and therefore can impact the patient journey and care.

Challenges experienced by parents accessing unlicensed medicines from community pharmacies were also reported by Wong *et al* (2006)(27) (study described in subtheme 2.4.3.1.2). A total of 216 carers took part in a telephone interview and it was found that 33% of participants had difficulties accessing their medicines in primary care. Nineteen participants explained how the community pharmacies did not store unlicensed medicines due to the often short expiry dates, and when an order was placed often pharmacies were unable to obtain the medicine needed due to not being able to find a manufacturer to provide the medicine in the first place, or manufacturers not creating the specific formulations

needed. The results further highlight specific issues with the availability of unlicensed medicines from the perspectives of parents or carers, again originating from inconsistent manufacturer access and supply.

### **Summary of subtheme**

Overall, the studies highlight the issues associated with a lack of pre-specified agreements to ensure consistent supply of all required formulations of unlicensed products from manufacturers, which were seen to cause treatment delays or disruption. This was often exacerbated by the short expiry dates associated with unlicensed medicines meaning they could not be stored within the pharmacies.

### **2.4.3.3 Theme 3 – Patient safety and patient care when receiving unlicensed medicines**

The factors identified that affected or could affect the patient journey or patient care when receiving unlicensed medicines included inconsistencies in the bioequivalence, formulations or doses of unlicensed medicines supplied, specific issues related to the safety of unlicensed medicines, and the role of patient/public awareness and acceptability of the use of unlicensed medicines. The study commentaries are outlined below.

#### **2.4.3.3.1 Inconsistencies in bioequivalence and formulation of unlicensed medicines and lack of robust evidence for determining doses in children**

A total of five studies explored the equivalence of, or inconsistent use of unlicensed medicines (6,10,13,29,45). This included examination of specific individual medicines, the variation between licensed and unlicensed alternatives and the scaling doses used for determining off-label medicines for children.

Chua *et al* (2016)(10), aimed to measure the release profile of melatonin from Circadin® tablets that had been divided or crushed (and therefore rendered unlicensed) compared to intact tablets. Unlicensed melatonin medicines in tablet and capsule forms were also used for comparison. It was found that the unlicensed medicines had a faster release profile and were more expensive than the licensed medicine, and the level of melatonin measured showed that unlicensed products had a greater deviation from the label strength compared with the licensed medicines, indicating they may not be bio-equivalent. The results highlight how crushed medicines or unlicensed alternatives may not be equivalent to the licensed product. The inconsistent bioequivalence of unlicensed medicines was also highlighted when compared not only to the licensed medicine but also when compared to differing formulations of the same unlicensed medicine.

This is supported by Mulla *et al* (2011)(6) who conducted an open label, single dose, three-treatment, three period, six-sequence crossover trial to assess the bioequivalence of liquid captopril formulations used in children. This involved 18 healthy adult patients aged between 18-55 over eight weeks. The authors suggested that the use of adults in testing the bioequivalence of different formulations even for children's medicines is an approach the regulatory authorities recognise as credible. The findings showed that the unlicensed liquid formulations were not bioequivalent to the licensed medicine, or even to each other. The formulations used did not produce any changes to the participants vital signs throughout the study, however three participants experienced a mild adverse event. Although the sample was relatively small, the results highlight that even when used in adults, the unlicensed medicines used in children are not bioequivalent to the original licensed products, and suggest equivalence issues between the varying formulations available for unlicensed medicines.

One study highlighted the large number of differing unlicensed formulations of captopril that were currently in use in the UK. Mulla *et al* (2007)(45) conducted a questionnaire survey to explore the variations in captopril formulations used for heart failure in children. The sample included pharmacists and technical staff at 13 cardiac centres and 13 large hospitals. The findings showed that four hospitals dispensed tablets for crushing or dissolving, the other 22 sites used nine different formulations of captopril. Of all the cardiac centres and associated hospitals only three were using the same liquid formulation with 10 centres and associated hospitals using different captopril formulations. In all but three hospitals, letters were provided to parents which provided details of where the medicines were sourced, and they were asked to provide these letters to the doctors or community pharmacy staff. The shelf life of these medicines varied from 1-2 weeks to 2-3 months. The study included multiple hospital and cardiac centres highlighting the wide variety of unlicensed captopril formulations used to treat children with heart failure.

The doses determined for children are often based on adult doses using scaling models, Johnson (2007)(29) aimed to compare three scaling models in determining doses for children from thirty medicines that were licensed or unlicensed for use in children to treat a range of conditions. The models based on body weight, 75% of body weight and body surface area were used to predict doses across paediatric age ranges for 30 drugs, which were then compared to the doses listed in the BNF for children. The findings showed that the body weight (0.75) and body surface area scaling models predicted doses that were 2.86 times higher than suggested in the BNF in the one month and one year old age groups. For the 7 year and 12 year old age groups, no predictions from any of the models were more than 1.8 times higher than the BNF recommendations. However, the body weight scaling

model seemed to under-predict the dose recommended across all ages. The results show that the scaling models used may not accurately predict doses for children and no model was found to be suitable across all paediatric age ranges.

The importance and impact on patient care of determining correct doses for children was highlighted by Mukattash *et al* (2011)(13). A survey was conducted in Northern Ireland to investigate the views of healthcare professionals on the use of unlicensed and off-label medicines in children. A total of 299 GPs, 168 community pharmacists, 36 hospital consultants and 65 paediatric nurses took part in the survey. Participants described concerns around the safety of the use of unlicensed medicines in children (77.8%) and the authors found that those who suggested the main reason for using off-label medicines were for doses lower than recommended, also experienced more treatment failures and those who reported the use of off-label was mainly for higher than recommended doses experienced more ADRs. The study provides a detailed look into the views of a range of healthcare professionals and highlights the risk on patient care when prescribers deviate from licensed products, that have been tested in trials for dose appropriateness and potential side-effects.

### **Summary of subtheme**

Overall, the studies have highlighted that unlicensed medicines are not necessarily bioequivalent to the licensed alternatives and that the different formulations of unlicensed medicines may not be bioequivalent to each other, which could impact patient care. Scaling models used to determine doses for children were found to result in some doses that were too high or too low for the patient, suggesting children may not be receiving optimal treatment.

#### **2.4.3.3.2 Safety issues associated with the use of unlicensed medicines**

A total of six studies explored the association between the use of unlicensed medicines and safety risks (3,4,5,7,17,30). More specifically medication errors, ADRs, mortality rates and the safety and efficacy of specific unlicensed medicines.

Conroy (2010)(7) conducted a prospective study and analysed reports of errors in a children's hospital to explore if there was an association between the licence status of medication prescribed and medication errors. A total of 158 reports were analysed and 55 prescribing errors were found, of which 15% related to products that were unlicensed and 7% to products that were prescribed off-label. There were a range of errors highlighted with incorrect doses being the most common. In terms of dispensing errors, 41% of errors were for unlicensed medicines and 23% for off-label medicines. In relation to administration errors,

21% were for unlicensed medicines and 21% were for off-label medicines. The errors reported were deemed to have caused no harm to patients in 87% of cases, however in 13% of cases the errors resulted in moderate harm. Of these, 60% of cases related to medicines that were unlicensed or off-label. The authors suggested that the use of unlicensed medicines in children is significantly associated with medication errors when compared to licensed medicines ( $p= 0.003$ ), with unlicensed and off-label medicines being associated with errors that can lead to harm. Although the results originate from one children's hospital site, and therefore may not be generalisable, the findings help to identify the types of medication errors that can be associated with the use of unlicensed medicines and highlight the implications of these errors on patient safety.

Four studies explored the use of unlicensed medicines in relation to ADRs, Turner *et al* (1999)(5) aimed to determine the incidence of ADRs as a direct result of administration of unlicensed and off-label medicines in paediatric wards at a children's hospital in Liverpool. Over a period of 13 weeks, a total of 4,455 medicines were prescribed for 936 patients over 1,046 hospital admissions. The findings showed that 3.9% of licensed medicines were associated with ADRs compared to 6% of off-label or unlicensed medicines. A clinical pharmacologist classified ADRs by severity and likelihood using pre-established criteria. Of the recorded ADRs, 17 had been classed as severe and of the 19 medicines involved in the severe reactions, 14 were off-label or unlicensed. Overall, the use of unlicensed or off-label medicines in paediatric wards were common, with 48% of patients admitted to the hospital receiving one or more unlicensed or off-label medicines. A significant association was made between the risk of ADRs and the numbers of medicines administered ( $p < 0.0001$ ). There was no significant association found between the use of unlicensed and off-label medicines and risk of ADR ( $p < 0.106$ ), however there was a significant association between the percentage of unlicensed and off-label medicines used and the risk of ADR ( $p < 0.0001$ ). Although the study was only conducted at one hospital, over 20 years ago and more recent evidence would be needed, the sample size was relatively large improving the validity of the significant findings reported.

In a more recent study, Bellis *et al* (2013)(3) conducted a nested case control study within a prospective cohort study, to explore whether the use of unlicensed or off-label medicines was a risk factor for ADRs in paediatric inpatients. Of the 1,388 patients included, 10,699 medicines were administered. The medicines with the greatest likelihood of resulting in an ADR (19%) were those that were licensed in children, but supplied outside of the licensed indication for age and weight. Additional medicines – unlicensed or licensed – increased the likelihood of ADRs, and specific medicines such as fentanyl when used off-label or in an unlicensed way led to ADRs in about 48% of cases. The authors concluded that the use of



unlicensed or off-label medicines were more likely to result in an ADR, with the number of medicines being administered also being a risk factor. The authors described the limitations they faced when conducting the study such as records outlining the specific preparations not always being available on prescription charts. However, the study had a large sample, which helps to increase the validity of their findings, and the findings do show unlicensed and off-label use as a risk factor for ADRs, and highlight increased rates of ADRs associated with the use of specific unlicensed medicines.

However, not all studies have shown a significant association between the use of unlicensed medicines and ADRs. Bellis *et al* (2014)(4) conducted a prospective cohort study on unplanned admissions to a paediatric hospital, in relation to the use of off-label and unlicensed medicines. A total of 6,020 unplanned hospital admissions were included in the study, and 14,923 medicines were administered to non-oncology patients, of which 71% were licensed, 24% off-label and 5% unlicensed. The risk of ADR was increased by 25% for each additional licensed medicine and 23% for each additional off-label or unlicensed medicine used. For oncology patients, 1,628 medicines were administered of which 57% were licensed, 34% off-label and 9% unlicensed. The patients who were most likely to receive an off-label or unlicensed medicine were neonates (57.3% of medicines prescribed). Overall, the use of off-label and unlicensed medicines was reported to be more likely to result in ADRs than compared to licensed medicines. However, as the use of oncology medicines resulted in many ADRs, and when oncology medicine results were removed, there was no significant difference in the risk between licensed, off-label or unlicensed medicines. The findings show an association between oncology prescriptions for unlicensed and off-label medicines and an increased risk of ADRs, but do not show an increased risk associated with the use of all unlicensed medicines.

The impact on patient safety associated with the use of specific unlicensed medicines was explored by (McAuley *et al.*, 2015)(17) who reviewed the drug related deaths database in Scotland to assess mortality related to psychoactive medicines in 2012. A total of 36 drug-related deaths were reviewed, of these 23 deaths recorded the use of Phenazepam®, an unlicensed benzodiazepine-type medicine and in 12 of these cases the use of Phenazepam® was reported to have been implicated in the actual cause of death. The authors acknowledge that the study involved a relatively small sample size, however the results show the impact unlicensed benzodiazepine-type medicines can have on mortality.

Although some studies were found to show increased risks when using unlicensed or off-label medicines, evidence has also been found that highlight their safe and effective use. Bagshaw *et al* (2020)(30) conducted a service evaluation to assess the safety and

effectiveness of unlicensed propofol-remifentanil mixtures for anaesthesia in children. Members of the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) TIVA Interest Group were asked to provide information on cases involving patients who had received the propofol-remifentanil mixture. Data was collected from 873 patients, and it was found that the propofol-remifentanil mixtures were most often used in procedures for gastroenterology or for ear, nose and throat conditions. Using the mixture was successful for all patients except for three, and serious adverse events were only present in 1.7% of cases. The findings show that in some cases the use of specific unlicensed products has been reported to be effective and relatively safe.

### **Summary of subtheme**

The findings highlight that as there are many different medicines that are considered unlicensed, some are clinically safer than others and that the safety risks associated with the use of unlicensed medicines are likely to be dependent on the specific medicine being studied, highlighting varying levels of risk.

#### **2.4.3.3.3 Patient/parent/carer and public awareness of unlicensed medicine use and perceived acceptability**

A total of ten studies included in the review contained information on the awareness of patients, their parents or carers and the general public on the use of unlicensed medicines and described how their perceptions of acceptability could impact the patient journey or care (8,11,12,13,20,22,26,33,39,41). When looking at patient awareness of the licensing status of their medicine, Donovan *et al* (2016)(11) as described in subtheme 2.4.3.1.2 conducted semi-structured interviews with prescribers, pharmacists and patients. Pharmacists described being reluctant to inform patients about the unlicensed status of their medicine, as it was perceived that the prescriber should be the person to inform the patient and that being informed by the pharmacists may damage the patient relationship with the prescriber. Patients agreed with this and reported how they would also like the pharmacist to inform them when supplying the medicine, which they admitted could be problematic had they not previously been informed by the prescriber. The study shows that healthcare professionals may have differing views on the responsibility to inform patients that they are being supplied an unlicensed medicine which may ultimately lead to some patients not being informed.

Healthcare professionals not informing the parents of patients that their child is receiving an unlicensed medicine is supported by Mukattash *et al* (2011)(13) as described in subtheme 2.4.3.3.1. Participants described concerns around the safety (77.8%) and efficacy (87.9%) of unlicensed medicines for children, and despite 85.4% of participants perceiving that parents should be informed when unlicensed medicines are prescribed for their children, only 30.7%

actually described informing parents. The results highlight that even though it is common for healthcare professionals to have concerns around the use of unlicensed medicines, this does not always translate to parents of patients being informed about the licence status of their child's medicine.

The rates at which patients were informed about the use of unlicensed medicines varied across studies. Ghosh, Arulrajan and Baldwin (2010)(39) conducted a retrospective case-note study to explore the use of unlicensed prescribing, data was gained from a single intellectual disability service over 12 years. The results consisted of medical notes for 114 patients, 66% of which received licensed medicines but for unlicensed uses, usually used for aggression and challenging behaviours. The records collected suggest that 80% of those receiving an unlicensed medicine were informed of this, directly or indirectly via their carers, showing patients were frequently informed in this population group.

The awareness of patients around the implications of receiving an unlicensed medicine was reported to directly impact continuity of care. Husain, Davies and Tomlin (2017)(26), conducted semi-structured interviews with parents and carers of children who received unlicensed medicines. Interviews took place four weeks after discharge from a London Children's Hospital. Telephone interviews were conducted with 15 parents or carers. Parents described several actions they felt they had to take to ensure they were able to receive a timely supply, such as increased contact with healthcare professionals, proactively seeking information about the medicine and planning and organising the process of ordering and receiving. However, needing to take on the responsibility for these actions caused worry for the participants. Although the study only included participants that were discharged from one hospital so presumably living in one area of the UK, the results strengthen the knowledge around the views and experiences of those receiving unlicensed or off-label medicines. The findings also highlight some of the challenges the carers faced and how pivotal it was for the parent or carer to be aware of the nature of the medicines prescribed in order to take on specific actions to ensure continuity of supply.

This is further supported by Wale *et al* (2020)(33) as described in subtheme 2.4.3.2.1, where interviews were conducted with community pharmacy staff. The pharmacy staff reported how patients receiving unlicensed medicines were required to take on additional responsibilities to ensure a seamless supply, such as informing the pharmacy or the GP in advance of when further supplies would be needed. Participants also described how, when a patient was not aware of the longer lead times required to access and supply unlicensed medicines, this led to a delay in the patient receiving the medicine, and could potentially result in treatment disruption and impact on patient care.

Patient or parental awareness of the differences in accessibility when receiving unlicensed medicines was also reported to impact the continuity of supply by Conroy *et al* (2020)(41) as described in subtheme 2.4.3.2.1. Of the 40 responses 22 participants were aware of parents facing issues when accessing further supplies of unlicensed medicines after discharge. Parental issues were reported, with a lack of awareness around the differences in availability and accessibility of unlicensed medicines when compared to licensed medicines, which caused treatment disruption, mainly when parents did not inform the GP in advance of when further supplies were needed. The findings further support the importance of patient awareness of the differences in accessibility when receiving unlicensed medicines and communication in ensuring that unlicensed medicines are received in a timely manner and highlight the potential disruption that can be caused due to a lack of awareness.

Acceptability of the use of unlicensed medicines by patients and the general public was highlighted in four studies. Venables *et al* (2015)(20) as described in subtheme 2.4.3.2.2, reported how sensory issues such as the taste of the medicine impacted paediatric patients' acceptability of the medicine and this included the use of a special medicine. The findings evidence that the actual medicine itself can impact patients' perceptions of acceptability, specifically in children.

Perceptions of acceptability around the use of unlicensed medicines was also explored in the general public by Chisholm (2012)(12) as described in subtheme 2.4.3.1.2. Whereas 47% of the public reported they would take an unlicensed medicine if there were no other options, 14% said they would refuse or be non-adherent if they were prescribed an unlicensed medicine if there was an alternative. Although 82% of the public reported trust towards their doctor, and 80% felt they made prescribing decisions with their doctor, 81% of participants described how they would have concerns about safety if the cost of the unlicensed medicines was the deciding factor to prescribe. The study shows that members of the public would trust the prescriber if the justification for an unlicensed medicine was based on their clinical needs, but concerns would increase if the decision to prescribe unlicensed medicines were based on cost. However, not all members of the public would accept being prescribed an unlicensed medicine, even if there were no alternative treatment options. The study did not differentiate whether acceptability varied depending on if the medicine was a 'special' or off-label.

Concerns of the general public were also reported when discussing the use of unlicensed and off-label medicines for children. Mukattash *et al* (2008)(22), used a survey questionnaire to explore the general public's views and awareness around the use of unlicensed medicines in Northern Ireland. Of the 1000 respondents, 86% were unaware about the use of

unlicensed medicines in children and 92% felt that parents should be informed of the licensing status when unlicensed medicines were prescribed. Whilst at the start of the study only 1.8% of participants felt that children's medicines were not safe, when informed about the use of unlicensed medicines within this age group perceptions changed, and the percentage increased to 64.2%. Participants also reported that they would be more likely to allow their child to participate in clinical trials if they had a life-threatening condition (41.9%) compared to if their child was healthy (3.9%). The study highlights a lack of awareness in the general public around the use of unlicensed medicines and increased concerns once informed, which would pose a barrier to recruitment in any trial attempting to establish safety of unlicensed products in children.

When exploring children's views on the use of unlicensed medicines for children Mukattash *et al* (2011)(8), conducted 16 focus groups with 123 school children aged 10-16 years in Northern Ireland. The findings suggested that the children felt that unlicensed medicines were unsafe and recognised that in order to reduce the number of unlicensed medicines used there need to be more trials to build the evidence for licensed medicines within this population. The children also described a trust towards the prescribers and their parents to make decisions regarding the use of unlicensed and off-label medicines but felt that parents and older children should be informed when unlicensed medicines are to be used. The authors recognise the results may not be generalisable, however the results provide the first look at the views of children in relation to the use of unlicensed and off-label medicines and again highlight the importance of trust in improving perceived acceptability.

### **Summary of subtheme**

The studies show the importance of patients or their parents and carers being aware they are receiving unlicensed medicines so that they can adopt a proactive approach towards managing their medicines, including adjusting to the differences in timelines involved in accessing unlicensed medicines in the community. However, it was noted that once informed, patients and members of the public had concerns over the use of unlicensed medicines, with some members of the public suggesting they would refuse treatment with such products.

## **2.5 Discussion**

The aim of this systematic review was to fully explore the factors that could affect the patient journey or patient care when receiving an unlicensed medicine in the UK. Results highlighted many factors reported to impact the patient journey from specific influences healthcare

professionals face when prescribing or supplying unlicensed medicines, to the safety of unlicensed medicines in general.

## **2.5.1 Exploring relationships in the data**

When exploring the factors that can affect the patient journey and patient care, the findings revealed specific challenges associated with the use of unlicensed medicines that were seen to impact the continuity of care across care settings, patient safety and provision of patient-centred care.

### **2.5.1.1 Continuity of care**

Continuity of care can be viewed from the patient or the healthcare perspective relating to an ongoing relationship between the patient and a healthcare professional and the organised clinical care that moves smoothly between different care settings (Gulliford, Naithani and Morgan 2006, RCGP 2011). The findings of the systematic review highlighted multiple instances where care had not moved smoothly between care settings and how the use of unlicensed medicines was specifically related to issues with organising and ensuring continuity of supply. As unlicensed medicines are made in smaller quantities than licensed medicines, they are often more costly (Griffith 2019) and the possibility of storing them can be limited by short expiry dates and often bespoke nature, resulting in longer lead times when accessing these medicines (Terry and Sinclair 2012). Pharmacists have described issues obtaining and storing unlicensed medicines (20) due to varying lead times issued from suppliers that were subject to change at any point, and an overall lack of consistent availability from multiple suppliers and in one case even from a hospital, which was reported to lead to treatment disruption (33). The lack of availability was also reported when interviewing carers (27), who described their community pharmacies being unable to identify manufacturers that could supply the medicine required or a lack of accessibility of specific formulations required. These issues identified by the review have been seen elsewhere in literature in relation to other medicines that also have short expiry dates and present similar challenges when trying to ensure continuity. One such example is medications for the treatment of cystic fibrosis, where difficulties have been reported by community pharmacists who have experienced interrupted supplies from manufacturers and by patients who have experienced delays to treatment (Herbert *et al.*, 2021).

Due to the challenges associated with the use of unlicensed medicines, healthcare professionals have an important role in ensuring the unlicensed medicine prescribed is suitable and that the supply is managed effectively to ensure continuity. However, multiple studies highlighted a lack of information or training for prescribers around how and when to use unlicensed medicines (2)(11)(27), which inevitably impacts their understanding. When

exploring the views and experiences of specialist clinicians (2) it was found that although awareness of the use of unlicensed medicines was high, a limited understanding of their uses for specific indications resulted in the prescription of a medicine that had previously been prohibited for use in pregnancy. The participants also expressed a desire for more guidance showing that even specialist prescribers feel as though they would want to increase their understanding when using unlicensed medicines.

To try and understand the perceived lack of confidence in relation to unlicensed medicines, it is important to note that there is no consistent undergraduate medical curriculum in the UK, only guidance on what learning outcomes need to be covered (Sharma, Murphy and Doody, 2019). This means that a range of subjects, clinical and non-clinical, will not have been covered consistently by all Higher Education Institutions (HEIs). Some examples from literature include variations in the length of urology placements during undergraduate training with some doctors reportedly having no placements in this area (Malde and Shrotri, 2011), variations between medical schools in how ophthalmology was included in the curriculum with differing teaching methods and assessments, with some students not receiving any training in ophthalmology (Baylis, Murray and Dayan 2011), gaps in teaching global health in medical education in the UK (Matthews, Davies and Ward, 2020) and variations in content covered and hours taught in relation to teaching medical ethics and law in UK medical schools (Preston-Shoot and McKimm 2010). Continuing from the undergraduate studies, the limitations of training for GPs in the UK have also been discussed within the literature relating to other matters, for example in treating paediatric patients (Modi 2016). In relation to screening for oral cancer, 97% of UK GP participants reported how they had never received training for screening for oral cancer and how this directly impacted their confidence to do so (Wade *et al.*, 2010).

The Royal College of General Practitioners (RCGP) have recognised the challenging role GPs have and how this had changed overtime, covering a range of clinical areas, and have repeatedly called for GP specialist training to be extended from three years to four years (RCGP 2012, RCGP 2017). The findings suggest that prescribers may not be effectively supported to manage the different areas of non-clinical and clinical care they may encounter and suggests a need for further training or increased guidance.

However, the guidance that is available for healthcare professionals has been found to contain inconsistent information even around the definitions for what unlicensed medicines are, in a study examining the content of 52 guidance documents used within the UK (Donovan *et al.*, 2018) (see 1.3.1). The wider lack of consistency of definitions provided within guidance documents and within the literature has been suggested to be potentially

confusing to healthcare professionals (Aronson and Ferner, 2017) and could reflect the limited understanding reported here. Inconsistencies in clinical practice guidelines have been reported elsewhere in literature. Some examples beyond unlicensed medicines include definitions of colorectal cancer treatment intervals (Molenaar, Winter and Slooter, 2021) and also inconsistencies in recommendations for the evaluation and management of hypertension identified in a systematic review (Alper *et al.*, 2019). The findings support issues identified in the literature and suggest a need for clear consistent information to be created for healthcare professionals to increase understanding of and support safe practice.

As a result of the limited understanding described above, studies have highlighted healthcare professionals relying on trust or the perceived expertise of others involved in the supply chain to support their practice decisions and reduce concerns. One study explored the views of a range of healthcare professionals and the results highlighted the importance of professional trust when supplying unlicensed medicines across care settings (11). This is supported by (33) interviews with community pharmacy staff who described a need to rely on the perceived expertise of prescribers, and how this helped to reduce their concerns when accessing and supplying unfamiliar unlicensed medicines and increase their perceived acceptability of the use of the medicine. This is also supported in the wider literature in a study exploring medication safety involving focus groups with community pharmacists, in which one participant described how they rely on the GP to have determined a suitable medicine and prescribed a dose that is safe for the patient, but how this was coupled with a concern that they could be blamed if the treatment were to cause any problems (Phipps *et al.*, 2009). This need to rely on the prescribing decisions of those higher up in the hierarchical structure of the healthcare system while still being responsible for their own practice could help to explain the varying perceptions of acceptability around the use of unlicensed medicine identified in the systematic review.

The acceptability of prescribers was reported to directly impact the way medicines are administered. Two studies explored the views of nurses who were responsible for supplying and administering unlicensed medicines to patients (14)(15). The results highlighted that the prescriber had a direct impact on how medicines were used, which resulted in medicines being crushed or opened despite there being liquid alternatives available (14). A small number of nurses said they would not question the prescriber even if they had no evidence for the use of the unlicensed medicine (15). The studies show that the nurses may trust the knowledge of prescribers, but some lack the confidence to challenge their decisions, again highlighting the impact of a limited understanding and the hierarchical structure within the NHS. The reluctance to challenge doctors' decisions has also previously been reported in literature. One example was provided by a study exploring nurses' perceptions in an acute



hospital, and reasons given for this included not wanting to cause conflict and stress, or due to worry over the outcome (Churchman and Doherty 2010). However, personal experience has been highlighted as an important factor that impacted nurses' decision-making in a literature review, with more experienced nurses feeling more confident to ask questions and implement interventions (Nibbelink and Brewer 2018).

The RCN (2020) highlight administration as a key aspect within the role of nursing, and outline that nurses should have an understanding of the medicine being administered, but do suggest that nurses can seek advice from pharmacists or prescribers when necessary. However, nurses like doctors are legally responsible for the care they provide to patients, as exemplified in a court case in which three nurses were charged with manslaughter along with a GP when a prescription medicine was administered to the wrong patient (Ferner, 2000). Although the healthcare professionals were eventually acquitted, the court case highlights the shared responsibility of healthcare professionals who prescribe and supply medicines to patients.

When looking at the evidence in relation to prescribers the limited understanding and need to rely on the expertise of others led to varying perceptions of acceptability around if and when unlicensed medicines should be used, with those in different roles describing differing levels of acceptability. Specific concerns reported by prescribers included the safety and efficacy of unlicensed medicines and concerns over their legal responsibility (12). It was also found that secondary care prescribers felt more confident in prescribing unlicensed medicines than those in primary care. This variation in confidence among roles was also reported within the literature when discussing individually tailored prescribing with nurse prescribers, GPs and pharmacists, along with a fear around not being able to defend prescribing decisions acting as a barrier to prescribing (Reeve *et al.*, 2018).

Two studies in the systematic review explored the views of GPs (28)(27) on prescribing behaviours. One study (28) found that the specific knowledge and speciality of individual GPs were seen to impact the prescribing of unlicensed medicines and other factors such as the amount of information received across settings, what the prescribing guidance states and their own specific concerns were also seen to impact their decision-making and therefore prescribing behaviour. This is supported by Wong *et al.*, (2006)(27) further GP explanations provided as to why they had decided not to prescribe specific unlicensed medicines when requested, which included the cost of the medicine, a lack of prescribing guidance or information on the medicine required and concerns over their own assumed risk. GP concerns over medico-legal risks is not specific to the use of unlicensed medicines and was found to be the reason why 12.5% of GPs had left their role in a survey conducted by

the GMC (GMC 2020a). Prescribers deciding not to continue prescriptions is also not unique to the use of unlicensed medicines. In one study, GPs described why they had decided not to continue prescriptions recommended by the London gender identity clinic, with reasons including a lack of expertise and feeling as though it was a specialised area of medicine (Legge and Seal 2019). The findings and wider literature further show how healthcare professional acceptability of the medicine requested and their own perceived knowledge can directly impact continuity of care.

It is important to recognise that GPs have the right to decide against prescribing an unlicensed medicine if they do not feel confident in its use, as they hold a legal responsibility when prescribing any medicine (GMC 2021). However, GP acceptability was seen to directly impact the continuity of care as when GPs had decided not to continue a prescription for an unlicensed medicine, pharmacy staff were then unable to supply the medicine to the patient despite feeling the use of the medicine was justified (33). This finding was also reported in another study (41) where pharmacists again described a lack of acceptability among GPs who were not willing to continue prescriptions for unlicensed medicines. Similar findings in Wales have been reported by Johnson *et al* (2012), who found an oncology consultant who described how a patient almost didn't receive treatment as the GP was unwilling to supply the medicine requested for the management of venous thromboembolism and advanced cancer. Although not related to the use of unlicensed medicines, the findings further show how GP lack of acceptability of the use of specific medicines can directly impact continuity of care. Issues with continuity of care such as the delays or disruptions caused by a lack of availability or as a result of healthcare professional perceptions of acceptability, can also have a direct impact on patient safety.

### **2.5.1.2 Patient safety**

The concept of patient safety is an important aspect of healthcare services that aims to reduce the chances of errors or harm that can occur when receiving treatment (WHO 2019b). The findings from the systematic review identified many issues with continuity that could impact on patient safety when receiving unlicensed medicines, such as inconsistencies in the medicines supplied. The inconsistencies in unlicensed medicines manufactured have previously been discussed in the literature, with differing excipients used to create the same medicine, resulting in varying expiry dates and storage needs (Rawlence *et al.*, 2018). One study explored the use of one specific medicine that had multiple unlicensed formulations available (45), and the results highlighted that 10 out of 13 hospitals and associated centres were supplying differing formulations with a total of nine different formulations available in just one area of the UK. This could directly impact patient safety as when unlicensed medicines were compared to licensed medicines, it was found the

unlicensed formulations were not bioequivalent to the licensed versions (10) or even to other unlicensed formulations (6). This variation in formulations is understandable as multiple manufacturers can produce unlicensed medicines but do not have to use the same excipients. When patients are discharged from secondary care into the community, community pharmacies do not have to use the same manufacturer as the hospital had done (Bourns 2017) which can explain the variation in formulations described within the literature. Community pharmacies consider prices when they obtain medicines from manufacturers as they receive a capped amount of funding each year from the NHS (Baird and Beech 2020). As such, no agreements are in place in current practice between prescribers and manufacturers to ensure the formulations remain consistent.

Another factor identified that could impact patient safety was the medicines used for children. As some medicines are not licensed for use in children, doses have to be determined using scaling models due to the pharmacokinetic differences across ages (O'Hara 2016) (see chapter 1). However, evidence was found that showed none of the scaling models assessed were suitable for determining doses across the paediatric ages (29). The impact of incorrect doses was highlighted by a range of healthcare professionals (13), who reported using doses that were higher than recommended and patients experiencing more ADRs, or reported using doses lower than recommended and patients experiencing more treatment failure. It is now recognised that children are at an equal, if not greater, risk of ADRs compared with non-elderly adults, with incident rates of ADRs causing hospital admissions varying from 0.4–10.3% (Smyth *et al.*, 2012), so any practice contributing to increasing the chance of ADR in children, such as the use of unlicensed or off-label medicines (Parry *et al.*, 2021), can have a direct impact on patient care and safety.

Altering the licensed formulation of medicines could also have implications on patient safety, for example the crushing of tablets or opening of capsules has been found to be potentially dangerous for patients if the medicine is intended to have an extended release (Gill, Spain and Edlund 2012). The RPS (2011) recognise many risks associated with altering medicines in these ways and suggest in most cases prescribing a ready to use unlicensed medicine, but also outline how uncoated, film-coated or sugar-coated medicines or immediate release medicines may be suitable for crushing if considerations about the medicines are made. A study included in the review (14) described high rates of crushing or opening medicines in nursing homes, and evidence was found to suggest that when this is done, the resulting medicine may not be equivalent to the licensed medicine (10). This suggests that the safety when crushing or opening medicines relies on the healthcare professionals' awareness and knowledge of the suitability of this method for the individual medicine. Although not highly associated with patient harm, a literature review highlighted some cases where medicines

were crushed despite manufacturers specifically stating the medicine should not be crushed or opened. The identified crushing of medicines has been found to be associated with problems such as contamination, spillage, and patients not taking the whole dose if crushed into food (Stubbs Haw and Dickens 2007), which could all impact patient care and the efficacy of the medicine.

There were many studies included in the review that explored directly the safety of unlicensed medicines. Evidence has been found to suggest an association between the use of unlicensed and off-label medicines and medication errors (7), however further evidence would be needed to support this. Of the four studies that explored the risk of ADRs when using unlicensed or off-label medicines, a range of results were found with some highlighting increased risks associated with the use of unlicensed medicines in general (3) or an increased risk associated with the use of specific unlicensed medicines such as Fentanyl (5) or oncology medicines (4) and even an increased risk of death when using unlicensed benzodiazepine-type medicines (17). The results show that there is inconclusive evidence from within the UK to suggest that the use of unlicensed medicines is associated with increased risks of ADRs in general, but that specific population groups who require the use of specific unlicensed medicines may be subject to an increased risk in relation to diminished patient safety. This potential for increased risk further supports the need for healthcare professionals to make careful considerations when deciding to prescribe or supply unlicensed medicines to patients, and the need for patient-centred care to reduce the chances of errors, delays or harm.

### **2.5.1.3 Patient-centred care**

Patient or person-centred care aims to take into account the views of the patient encouraging autonomy and offering choice (NWSSP 2021), by providing the education and support needed for patients to be involved in their own care so that treatment can be centred around the patients' needs (WHO 2015). Patient-centred care may be especially beneficial to patients who receive unlicensed medicines, which often have short expiry dates and may not be as accessible as licensed medicines, as described above.

Many patients have a justified need for the use of unlicensed medicines and the results of the systematic review outline multiple instances of this, including when prior treatment with licensed medicines was unsuccessful or led to allergic reactions (16), when treating a rare condition for which there were no licensed treatments available at the time (18), and in one case the use of an unlicensed veterinary medicine was required for human use (25). The use of unlicensed medicines described within this literature is in line with the MHRA guidance (MHRA 2014a) that outlines how unlicensed medicines should only be used when

there are no suitable licensed alternatives available. There are circumstances where the decision to not prescribe an unlicensed medicine is justified and in the patients' best interest, if it is not deemed to be the most suitable option. However, when there are no alternatives available and the prescription is not continued, this can disrupt the continuity of care and by extension, care is not patient-centred. This is not in line with the AWMSG's five-year strategy (AWMSG 2018), or the Welsh Government's plan for 'A Healthier Wales' (Welsh Government 2021b), which aim to provide seamless care for patients across care settings. Examples of seamless care in practice have been reported by the Welsh NHS confederation (2018), whereby the use of multi-disciplinary team meetings were piloted in three GP surgeries in 2017 to improve care for the elderly in the community. The healthcare professionals involved described the benefits of this approach including increased communication, decreased times for referrals, improved awareness of individual roles and increased co-ordination between services that helped to save time. This approach may also be suitable for care of patients where management with unlicensed medicines is required.

Specific treatment groups such as in intensive care (40), palliative care (42) or those patients with affective disorders (9) were highlighted in the systematic review as receiving unlicensed medicines. However, the majority of reasons for prescribing unlicensed medicines were related to age, with many studies specifically looking at the use of unlicensed medicines in children (19,21,23,24,34,35,36,37,38,43,44), where there is either a lack of available licensed medicines, or the licensed medicines available are not suitable for children who required different doses or formulations for use. It has been suggested that children are more likely to receive unlicensed and off-label medicines compared to other population groups, as clinical trials are not usually conducted in children (Hilmer and Gazarian, 2008). The lack of clinical trials in children has been recognised as an issue within the literature for many years (Joseph, Craig and Caldwell 2013). The importance of clinical trials in children has also been highlighted many times within the literature as children are not little people and therefore determining doses from clinical trials conducted in adults can be potentially dangerous (Naka, Strober and Shahriari, 2017). The benefit of clinical trials in children in ensuring the safety and efficacy of medicines has been evidenced recently in the UK, when the MHRA granted authorisation for the use of the Pfizer vaccine for Covid-19 in children aged between 12-15 in June 2021 after a tailored clinical trial in children had shown the vaccine to be safe and effective (Welsh Government 2021c). There have also been initiatives to increase the involvement of children in research, for example the National Institute for Health Research have released a set of standards for public involvement, which places importance on creating inclusive opportunities and working together (NIHR 2019). The NIHR also highlight the benefits of involving children to improve the design and delivery

of clinical research for children (NIHR 2021). By increasing children in the involvement of clinical trials and research, more medicines can be licensed for use across the different ages and therefore provide patients with patient-centred care.

The findings of the systematic review suggest even further that patients are not at the centre of care when receiving unlicensed medicines, as they were not always informed of the licensing status when unlicensed medicines were supplied. As patients would not normally know which medicines are unlicensed, they would need to be informed. However, two studies included in the review found varying reports of how often this happens (13)(39). In a study looking at GPs experiences only 30.7% reported informing patients (13) compared to another study in which 80% of patients were informed by a disability service (39). Although there were only two studies that reported informing patients the results suggest that patients are not consistently informed when they are receiving unlicensed medicines. One study reported that pharmacists may also be reluctant to inform patients that they have been prescribed an unlicensed medicine, as it was perceived by pharmacists to be the original prescribers' responsibility (11). However, the RPS (2016) outlines that medical prescribers and pharmacists conducting clinical check and dispensing both have a responsibility when prescriptions for unlicensed special medicines are provided to patients, to ensure not only that the use of the medicine is needed but also to support patients, showing there is a shared responsibility when prescription medicines are supplied.

The evidence to suggest patients are not informed and the reluctance described above may also be attributed to concerns that have been reported by patients and the general public within the literature. Three studies explored the general public's views on the use of unlicensed medicines, with one finding a lack of awareness about the medicinal licensing process and highlighting how, once parents or carers were informed about the use of unlicensed medicines for children, their concerns rose from 1.8% to 64.2% (22). Even children were reported to perceive the use of unlicensed medicines to be unsafe, although they would trust the doctor and their parents' decision if they were told they required an unlicensed medicine (8), and one study found that 14% of the general public would refuse or not adhere to treatment if they were prescribed an unlicensed medicine (12). Non-adherence has been highlighted by WHO (2003) as a global issue, with around 50% of people with chronic conditions not adhering to their treatment schedule in developed countries, however it is unclear what percentage of people choose to refuse treatment altogether, compared to intentional or non-intentional non-adherence.

The findings show that patients and the public may also have varying perceptions of acceptability around the use of unlicensed medicines and further emphasises the need for

patient-centred care so that patients can be informed when they are to receive an unlicensed medicine while addressing any concerns that may arise, and reducing the likelihood of non-adherence or refusal.

However, the reluctance to inform patients could also be a result of the guidance available to healthcare professionals, providing inconsistent details around whether patients should be informed of the licensing status when prescribed unlicensed medicines. Some guidance outlines that patients should be informed in all cases (BNF 2021b) whereas others acknowledge the potential of informing patients to lead to concerns and suggest that prescribers may not always want to bring attention to the fact the medicine is unlicensed (AWMSG 2021). The findings further suggest a need for consistent information to be created for healthcare professionals to ensure patients are consistently informed without causing concerns. Although the results acknowledge that informing members of the public and patients about the use of unlicensed medicines may lead to an increase in concerns and that some patients may refuse treatment, if they are not informed they cannot provide informed consent. If patients are not aware of the fact they are receiving unlicensed medicines or of the associated implications of this, they would not be able to be involved in decision making and by implication receive patient-centred care.

Despite the reluctance and concerns described above, the findings of the systematic review highlight the importance and need to inform patients when receiving unlicensed medicines, as pharmacists described how these patients are required to take on increased responsibilities to ensure they can access treatment (33). These responsibilities included informing the pharmacy in advance of when supplies were needed to manage extended lead times and short expiry dates and participants described an experience where delays were caused when the patient did not take on the responsibilities successfully. The need for the patients to take on increased responsibilities when receiving unlicensed medicines was also reported by the parents or carers of children who required them (26), this included the need for increased contact with the pharmacy and organising supply. The impact of patient awareness and successfully taking on responsibilities was also supported by (41) pharmacists who described how patients' lack of awareness around the accessibility of unlicensed medicines led to a delay in informing the GP the prescription was needed, and resulted in treatment disruption. The lack of consistency in how patients are informed, and the direct impact patient awareness can have on continuity of care suggest the need for the creation of a consistent information leaflet for patients.

As patient information leaflets are not commonly available for individual unlicensed 'special' medicines (RPS 2016), information could be created for all patients who receive unlicensed

medicines to outline their medicine is unlicensed without causing concern, but also to ensure they can take on the increased responsibilities around managing the extended lead times. An example of this has been produced by Oxford University hospitals (NHS 2016) where information around what unlicensed medicines are is provided, reassurances around the safety are given and the increase in lead times acknowledged with suggestions of how the patient could manage this. However, it is unclear how often information leaflets like this are used within practice and as many other patient information leaflets for unlicensed medicines exist with varying content (HERPC NHS 2017)(Medicines for Children 2020), even when leaflets are provided, patients may not receive the same amount of information. To better understand the information given to patients, further research is needed to explore how healthcare professionals approach informing patients and to explore patients experiences around how they were informed or what they would like to know.

The value of patient information leaflets has been recognised as they provide the patient with information that can be taken home and looked over again as information may not be taken in during the typically short consultations between patient and doctors and supports informed decision-making (Scot Public Health 2020). However, the content of the information leaflets can impact patient perception. Focus groups were conducted with patients who reported emotional responses to how information about associated risks were presented and the authors suggest that when creating information leaflets considerations should be made to ensure the language is not frightening for patients (Herber *et al.*, 2014).

Involving patients in the creation of information has been suggested to aid the creation of good quality information leaflets (Herber *et al.*, 2016) and could help to identify ways in which patient-centred care can be improved for patients receiving unlicensed medicines. Dickinson, Raynor and Duman (2001) compared patient views on two patient information leaflets, one created using the European Commission (EC) model for leaflets and one based on best practice in information design (Mark II). The patients reported issues with both the leaflets created, including difficulties understanding the content. The authors conclude the benefits of involving patients in the development of information leaflets to ensure they are patient friendly and can effectively inform patients.

By gaining further evidence around the views and experiences of healthcare professionals and patients involved in the use of unlicensed medicines, areas where increased support is needed can be further identified, along with any potential factors that could affect the patient journey that have not been identified previously within the literature.



## **2.5.2 Assessing the robustness of the synthesis**

### **2.5.2.1 Strengths and limitations**

In terms of study limitations, the researcher acknowledges their own influence in creating the search strategy and inclusion criteria and accepts that this can impact the outcome of the results. Another limitation identified was that the included studies varied in designs, aims, and methodologies, making it difficult to compare across studies (see 2.3.8). The included studies also differed on how results were presented with some combining evidence for unlicensed and off-label medicines and others presenting results separately.

A number of studies identified throughout the searching process could not be accessed as full copies by the researcher or were not available as full papers. Where possible, the researcher reached out to authors in the hopes of obtaining full reports however, in many cases these requests were not responded to, or the authors confirmed that a full paper of the results was yet to be published. This suggests that many studies identified in the databases searched may have provided valuable evidence that could contribute to the existing knowledge, but as full reports were unavailable or non-existent, they could not be included in the review.

In terms of strengths, a robust process was ensured through regular meetings with a University subject librarian to discuss and strengthen the search strategy used, and by using evidence to guide the selection of databases to ensure reliable results. The search strategy and screening criteria were also reviewed by the academic supervisor and a number of abstracts (25%) were screened and compared by the researcher and the academic supervisor to ensure the screening criteria was effective in only selecting relevant information.

The researcher also used the PRISMA checklist to structure the chapter in the aim of producing a well-rounded and replicable report, and conducted a quality appraisal process using validated checklists resulting in each included study being assessed for quality. The quality appraisal results can be seen in Appendix 3).

Lastly, as the Cochrane library, the Joanna Briggs Institute EBP Database and PROSPERO had all been searched for any similar systematic reviews, to the researcher's knowledge this systematic review provides the first review of the evidence related to the factors that can affect the patient journey and patient care when receiving an unlicensed medicine in the UK.

### **2.5.2.2 Reflections**

The researcher developed many different skills throughout the process of conducting a systematic review. Creating a research question and developing a search strategy that could

effectively find the most relevant information required some trial and error while conducting scoping searches to identify the most suitable strategy. Conducting the searches provided the researcher with experience using multiple databases and understanding how to use the differing proximity and boolean operators available.

The researcher reflected on the number of papers identified that were only available as abstracts and perceived the importance of writing up findings in full papers to ensure the evidence gained can be used in combination with similar studies. Without a full publication of results and no way to quality assure the methods, the researcher had to exclude potentially valuable findings. Despite this, the researcher felt the results of the review helped to explore the available existing literature and provided a detailed insight into the factors that have been reported to affect the patient journey and care when receiving an unlicensed medicine in the UK.

### **2.5.3 Summary / Conclusion**

To the researcher's knowledge, this is the first systematic review to explore the patient journey as a whole in relation to the use of unlicensed medicines, and as such provides a unique insight into the factors that can impact the decision to prescribe an unlicensed medicine through to accessing the medicine after discharge. Overall multiple factors were seen to impact the patient journey and patient care when receiving an unlicensed medicine, some of the key factors identified included the specific challenges associated with the use of unlicensed medicines such as differences in accessibility and the potential for increased risks. The varying acceptability of prescribers around the use of unlicensed medicines was seen to delay treatment across care settings or to directly impact how unlicensed medicines were used when others relied on the prescribers' perceived expertise.

The implications of the findings suggest that increased guidance around the use of unlicensed medicines should be created and provided to healthcare professionals to increase the level of acceptability and reduce uncertainty about suitability across care settings. The findings also suggest that detailed information about prescriptions for unlicensed medicines should be transferred to all those involved in the supply chain to reduce the chance of errors or delays. Increasing awareness of the use of unlicensed medicines in patients and the general public in a way that would address concerns could also help to reduce delays as it would support patients taking on increased responsibilities when managing supplies. The lack of availability of certain products will be a difficult factor to overcome as unlicensed 'special' medicines cannot be advertised, however the health board could supply lists of suppliers who sell unlicensed medicines to community pharmacies to

reduce the workload of sourcing where the medicines could be obtained and the risk of delay or inconsistencies in the medicines supplied.

### **2.5.3.1 Next steps**

There was a limited number of studies that specifically explored the views and experiences of those involved in prescribing, accessing, supplying, and receiving unlicensed medicines, and none solely conducted in Wales, where the responsibility for NHS Wales lies within the Welsh Cabinet Secretary for Health and Social Service after devolution. Further research in this area is needed to better understand the complex interactions and specific issues that may not have been highlighted in the literature so far, or may be specific to Wales. The aims of the studies in this thesis will contribute towards addressing this evidence gap and will provide further evidence for factors that could affect the patient journey and patient care when receiving an unlicensed medicine in Wales.

## **3. Methodology**

### **3.1 Overview of chapter**

The results from the systematic review conducted and presented in Chapter 2 highlighted areas for further research and shaped the development of the methodological approach presented in this chapter.

Within this chapter the research paradigm, design and approaches selected to address the research aims will be outlined. To do this, a description of a range of research paradigms or worldviews will be provided and discussed in terms of suitability to the project, along with the assumptions they encompass. This will be followed by a detailed description of qualitative, quantitative, and mixed method research designs and approaches, and the suitability of each method to meet the aims of the studies included in the thesis will be reviewed.

Sampling techniques will also be discussed in relation to the different designs and again in terms of what is most appropriate to address the project aims. An explanation for why each design or method was selected will be provided.

The researcher characteristics and reflexivity will be discussed in relation to the research project, and the researcher will outline the techniques used to enhance trustworthiness. This will be followed by a description of the engagement had with stakeholders throughout the research process, how this was achieved and the impact this had on the research. Lastly, ethical considerations will be addressed such as informed consent, confidentiality, anonymisation, peer review and ethical approval.

### **3.2 Philosophical worldviews**

Philosophical worldviews or research paradigms describe a set of assumptions or beliefs about reality and truth that inform the appropriate approaches and methods selected when conducting research (Fossey *et al.*, 2002; Scotland 2012). These beliefs relate to multiple factors including how we see reality (ontology), how we know what we know (epistemology), and how we conduct the research (methods) (Creswell, 2007). All researchers bring a worldview and corresponding set of assumptions to the research process (Creswell 2014). To improve credibility, it has been suggested that the author should acknowledge and outline their philosophical worldview along with the ontological and epistemological views that establish the researcher's analytic lens (Caelli *et al.*, 2003).

The ontological position relates to the view and nature of reality (Guba and Lincoln 1989), and the epistemological position relates to how truth about this reality can be known in relation to the individual (Killam 2013). There are multiple research paradigms with varying

ontological and epistemological approaches that provide different outlooks and perspectives (Guba and Lincoln 1994). The research paradigm for a specific study needs to be selected based on what is considered most relevant to the research question and aims. When considering the use of unlicensed 'special' medicines in the UK there are laws, regulations, and a plethora of information about the requirements healthcare professionals must abide by when supplying unlicensed 'special' medicines to the public. However, there is little information available about how they perceive this process or the impact these processes have on the patients' experience.

This chapter will explore four commonly adopted research paradigms: positivism, post-positivism, interpretivism (constructionism) and pragmatism. A brief description of these paradigms will be provided along with an explanation of the considerations of the relevance of the outlook to the research questions and aims.

### **3.2.1 Positivism**

Positivism views reality as one single reality, with an objective truth that is separate from participants or researchers (Park *et al.*, 2020) and primarily uses quantitative methods to record or measure this truth (Aliyu *et al.*, 2014). Positivism has long been used within healthcare research, for example in the use of randomized control trials (Broom and Willis 2007), however as the aim of this research was to gain a better understanding of the individual views and experiences of healthcare professionals and patients around the use of unlicensed 'special' medicines, the ontological and epistemological view that there is only one reality that is objective to the individuals involved, was not suitable. As these participants are likely to hold differing views and would have inevitably had differing experiences related to the use of their medicines, this paradigm was not best suited to address the research question.

### **3.2.2 Post-positivism**

Post-positivism, like positivism has a realist ontological position and views reality to be external, but the epistemological view recognises that this reality is always being interpreted through social conditioning and therefore may never be fully gained (Ponterotto 2005; Weaver and Olsen 2006). This paradigm is better suited to the research aim by acknowledging the impact of social influence on how reality is perceived. However, again as our aim was to explore the individual perceptions and experiences related to the use of unlicensed 'special' medicines and therefore individual realities, the ontological position adopted within this research paradigm was not in line with the research question and aims.

### **3.2.3 Interpretivism**

Interpretivism, otherwise known as constructivism, moves away from a realist ontological position and accepts a relativist view (Guba 1992), assuming that reality is constructed through peoples' experiences in life and how they are internally perceived and interpreted. In this way the constructed reality may vary between individuals (Becker, Bryman and Ferguson, 2012) and the truth gained is subjective (Wahyuni 2012). The interpretivist paradigm has been used previously within healthcare research to explore patient views and experiences across care settings (Toscan *et al.*, 2013) and doctors' experiences around prescribing specific types of medication (Mattick *et al.*, 2014). The ontological and epistemological perspectives of this paradigm would allow the researcher to gain individual views and experiences of participants who prescribe, access, supply or receive unlicensed 'special' medicines, and as such, was seen as the most suitable outlook for the research.

### **3.2.4 Pragmatism**

Pragmatism accepts both versions of reality as described above, suggesting that there is one objective and multiple subjective realities and sees this as "*two sides of the same coin*" (Morgan 2014 pg.1048). Pragmatism as a research paradigm typically uses mixed method approaches to gain information about both realities, selecting methods to best target the individual research questions and aims in the hopes of improving the real world (Bishop 2015). Although pragmatism has been used in healthcare research (Shaw, Connelly and Zecevic 2010), as the primary aim of this study was to get a better understanding of the individual views and experiences of those involved in the use of unlicensed 'special' medicines, and as such their individual subjective realities, the researcher decided against this research paradigm, for this specific research project.

The researcher appreciates the pragmatic research paradigm believing that the outlooks and approaches selected should be determined based on the research question and aims and sees all of the paradigms discussed above as useful for different contexts within research. As the primary aim of the studies included in the thesis is to gain a better understanding of views and experiences of participants, the researcher viewed a constructivist outlook to be most suitable to address the research question.

## **3.3 Qualitative approaches and methods**

Qualitative research focusses on how people interpret the world and the experiences they live through (Holloway and Galvin 2016). By collecting words rather than numbers, qualitative methods are often used to explore under researched topics (Mauk 2017) in an

exploratory way to gain an insight into beliefs and attitudes, and to understand meaning from the participant's point of view (Hammarberg, Kirkman and De Lacey, 2016). In this way, qualitative methods allow the participant voice to be gained and help to identify why participants feel the way they report and how this relates to their behaviour (Sutton and Austin, 2014). As the research aims to better understand the views and experiences of multiple population groups, a qualitative study was well suited as a methodological approach.

Qualitative approaches have been used across many fields including health research and have greatly improved our understanding of how societies and individuals perceive and cope with health and illness throughout life (Green and Thorogood 2018). For example, understanding behaviour around medical adherence (Sankar 2006; Santer *et al.*, 2014), gaining insights into the experiences and reactions of patients to specific life-threatening conditions (Hunter *et al.*, 2017) or views in relation to the services patients receive with the aim of quality improvement (Pope, Royen and Baker, 2002). There are multiple approaches that can be used when conducting qualitative research; a brief outline of five commonly used approaches within health research (Creswell 2007) will be given below and their suitability for this research will be discussed.

### **3.3.1 Ethnography**

Ethnography focusses on behaviours and beliefs from a cultural perspective (Fetterman 2009), the different population groups involved in the research could be considered different cultural groups, however ethnography typically involves observing and studying participants within the environment under study (Roberts 2009). This type of approach would not provide detailed data about the participants' own perceived views and experiences and as the study planned to recruit across multiple care settings throughout Wales, was determined to be impractical for this project.

### **3.3.2 Grounded theory**

Grounded theory focusses on the behaviours and beliefs of individuals and uses this information with the aim of creating a theory to explain it (Stern and Perr 2011, as cited in, Ivey 2017). In this way the theories created are rooted in the data collected (Strauss and Corbin 1994). This approach would help to identify the views and experiences of individuals however, as this project was not looking to develop theories based on the results but rather have more of an exploratory design, this approach was seen as not suitable to address the specific research aims.

### **3.3.3 Case studies**

Case studies focus on a specific complex situation in its actual setting (Crowe *et al.*, 2011), typically involving a limited number of participants or organisations (Rowley 2002). As the research project aimed to explore the individual views and experiences of participants across multiple care settings and across all seven health boards in Wales, this method was also deemed not to be suitable, as it would be too time-consuming to complete and would not allow for in-depth discussion with participants.

### **3.3.4 Phenomenology**

Phenomenology focusses on a specific experience from the perspective of the individuals who have lived through it (Byrne 2001) and is typically used to study under-researched areas (Donalek 2004). This approach often involves detailed exploration into individual experiences (Starks and Brown Trinidad 2007), as this study had specific population groups in mind, and focussed on understanding the views and experiences of individuals around the use of unlicensed 'special' medicines, a phenomenological approach was considered to be the most suitable approach.

### **3.3.5 Data collection methods used in qualitative research**

The main methods used to collect data in qualitative research are observational, interviews, and focus groups (Coast 2017). The selected methods need to be guided by the research questions, as this research aimed to get an in-depth understanding of the views and experiences of those involved in the use of unlicensed 'special' medicines, some methods were deemed more suitable than others.

#### **3.3.5.1 Observational methods**

Observational methods, which are either conducted overtly where the participant is aware they are being observed, or covertly where they are not, are often used within healthcare research, and mainly focus on observing peoples' behaviours and interactions within a certain setting (Mays and Pope 1995). Observational studies have been conducted to identify communication patterns among staff in hospitals (Coiera and Tombs 1998), between patients and healthcare professionals (Manias *et al.*, 2019), or to study specific behaviours such as hand washing by healthcare professionals (Watanakunakom, wang and Hazy 1998).

Although the use of observational methods would help the researcher to learn more about the processes involved around the use of unlicensed 'special' medicines, there were certain practical issues and challenges related to this method. For example, observation would be a time-consuming process, the researcher would have to travel to multiple pharmacy sites, GP



surgeries and hospitals to observe a large number of interactions in order to gain an adequate amount of information required, and the Hawthorne effect has shown that observing practice directly may also impact the behaviours of those involved (Sofaer 1999; Sedgwick and Greenwood 2015). Observational methods can be an extremely valuable tool when trying to understand a phenomenon of interest but does not allow for the exploration of cognitive processes such as an individual's reasons for or against prescribing unlicensed 'special' medicines. As this method does not focus on gaining a detailed insight into the individual views and perceptions of participants, this method was not deemed an appropriate or practical means of meeting the aims and objectives of the studies in this thesis.

### **3.3.5.2 Interview methods**

Interviews are the most common data collection method in social and health sciences research (Gill *et al.*, 2008) and include focus groups, structured, unstructured, or semi-structured interviews. Interviews are well suited for the studies in this thesis, as the aim is to gain a better understanding of the views and experiences of individuals involved in the processes of prescribing, obtaining, supplying or receiving unlicensed 'special' medicines. Both the use of focus groups and one to one interviews would allow the researcher to gain an understanding of peoples' views and experiences across care settings, but there are some key differences between these methods.

Focus groups are useful for gaining views and perceptions from groups of people at one time, potentially saving time and expenses while allowing interactions between participants (Longhurst 2003). As the studies in the thesis aim to collect data from across Wales, data collection would largely be conducted remotely, theoretically making focus groups a suitable method of data collection. However, there would be significant challenges of managing dynamics of multiple participants online, and difficulties arranging suitable times for multiple participants, specifically in the healthcare professional sample. Specific disadvantages associated with the use of online focus groups have been reported within the literature. This includes technological challenges, requiring all participants to have a high-speed internet connection, and it has also been suggested that participants may be more likely to drop out of online focus groups as they have not made a verbal commitment (Stewart and Shamdasani 2017). It is also recognised that interviewing in groups can influence the views presented by participants and the results may not be representative of the individuals involved or as in depth as results from one to one interviews (Stokes and Bergin 2006). One to one interviews also have the added benefit of being able to be easily conducted online or over the phone, and as such are able to recruit participants from a wider geographical area increasing the chances of a more representative sample (Rosenthal 2016). As the studies in the thesis aim to gain a detailed understanding of the views and experiences of specific

individuals rather than a consensus, the use of focus groups would not have met the aims of the studies, and one to one interviews were deemed to be a more appropriate method.

One to one interviews can be conducted in a structured, unstructured, or semi-structured manner, depending on the type of information being studied. Structured interviews typically contain a fixed set of questions that all participants are asked, limiting the range of responses but potentially reducing the interviewer bias and creating more generalisable findings (Qu and Dunmay 2011). Unstructured interviews have very little structure to the interview and look to explore topics for which the answers cannot be predetermined and in which the interviewer primarily listens to the narrative being provided by the participant (Leavy 2014). This method allows the participant to raise themes that may not have been anticipated by the researcher and each interview can produce largely varying results with differing structures and key findings (Zhang and Wildemuth 2009).

Semi-structured interviews allow the researcher to guide the interview while also allowing flexibility such that each participant's interview can be varied, which will result in a detailed account of each individuals' experiences and feelings to be formed (Miles and Gilbert 2005). Conducting the interviews face-to-face, where available, also allows the researcher to take any observations, such as tone of voice and body language, into account (Opdenakker 2006). Due to the range of unlicensed 'special' medicines available and the lack of standardisation of approaches to each step of the patient journey highlighted by our findings in the systematic review described in chapter 2, it would suggest that patients and healthcare professionals may have largely differing experiences and perceptions about the medications. Taking this into consideration, semi-structured interviews were adopted instead of structured or unstructured interviews, to allow the researcher to ask about the individual stages involved in the use of unlicensed 'special' medicines, while also allowing the participants to raise topics of importance to them potentially identifying unanticipated views or experiences.

### **3.3.6 Sampling in qualitative research**

#### **3.3.6.1 Sampling methods**

There are a multitude of strategies and techniques used when sampling in research, these are often split into probability sampling and non-probability sampling. As probability sampling usually aims to gain a representative sample so that results can be generalised to the rest of the population (Omair 2014), it is not well suited to qualitative research (Pope 2002) such as the research described in this thesis that aims to gain a detailed insight into a small number of individuals' views and experiences.

Non-probability sampling involves methods where participants are not selected based on probability but by other means (Vehovar, Toepoel and Steinmetz 2016), four of the commonly used non-probability sampling methods, (convenience, snowball, quota and purposive sampling) (Elliot *et al.*, 2017) will be described below.

#### **3.3.6.1.1 Convenience**

Convenience sampling involves recruiting participants that are convenient for the researcher to recruit in terms of availability and accessibility (Etikan, Musa, and Alkassim 2016; Elfil and Negida 2017). Often used in clinical research, this method of sampling is an affordable approach and allows for the recruitment of any potential participant that fits the eligibility criteria, although this may result in a biased sample with ungeneralisable results (Acharya *et al.*, 2013). As the methods selected for the studies in this thesis do not aim to gain generalisable results, but rather to shed light on the views and experiences of specific individuals, this method was deemed as a potentially useful sampling strategy.

#### **3.3.6.1.2 Snowball sampling**

Snowball sampling involves using social networks to recruit participants (Noy 2008) by asking each participant in the sample to identify others who may be eligible to take part, and this process continues for the newly identified participants and so on (Goodman 1961). As with convenience sampling, this approach can lead to bias in the sample gained as the participants know each other so would be unlikely to produce a random sample (Parker, Scott and Geddes 2019). However, by using the social networks to identify participants the researcher can access groups that would have been difficult to identify, without the need for a large amount of time or resources (Cohen and Arieli 2011). As the studies in this thesis involve recruiting participants across Wales this method would be useful for accessing populations in smaller areas where it may be harder to disseminate information.

#### **3.3.6.1.3 Quota**

Quota sampling aims to gain a sample that is representative of and proportionate to the population being investigated (Sharma 2017). This can be useful when trying to determine subgroup differences, but would require a relatively large sample to gain enough information about the different subgroups in the population and can be more expensive than other methods (Bornstein Jager and Putnick 2013). However, as there would be no way to know the sociodemographic factors about the populations involved in the studies in this thesis, (e.g. age and gender of patients receiving unlicensed medicines), without having access to patient records or personal information, a quota sample would not be practical and as the researcher aimed to conduct in-depth semi-structured interviews would be too time consuming to gain a suitable enough sample.

#### **3.3.6.1.4 Purposive sampling**

Purposive sampling involves the researcher selecting participants based on their knowledge and experience with the topic being studied, for example when studying a specific phenomenon to identify and select experts of that field to address the research question (Marshall 1996; Tongco 2007). In this way the researcher will purposely choose those participants who can provide the best perspective offering valuable insights into the topic being studied (Abrams 2010; Robinson 2014). As with most of the non-probability sampling methods, this approach does not provide data which can be generalised and is subjective, however it is valuable when conducting exploratory research (Taherdoost 2016). The studies in this thesis are exploratory studies looking to gain an insight into the views and experiences of specific individuals related to the process of prescribing, accessing, supplying, and receiving unlicensed 'special' medicines and as such, purposive sampling would be suitable for selecting participants who would have had experiences around this.

Many of the approaches outlined above were deemed as suitable for the studies in this thesis and as such a mix of sampling approaches were adopted, the specific methods and details around how they were used are outlined in the individual study chapters (see chapters 4,5,6).

#### **3.3.6.2 The role of gatekeepers in sampling and recruitment**

Gatekeepers have an important role within research, aiding the researcher in gaining access to potential participants. This is especially important when trying to access participants within the NHS, where the researcher cannot identify and contact participants directly (Wiles *et al.*, 2005). Contacting and maintaining interactions with gatekeepers can be challenging, however gatekeepers can play a valuable role in facilitating the research process and ensuring access to specific sites and participants (McFadyen and Rankin 2016), resulting in useful and usable results (Clark 2011).

When trying to ensure successful recruitment, it has been suggested to identify and work with gatekeepers who are trusted by the participants, and by conducting recruitment in person within the clinical setting (Namageyo-Funa *et al.*, 2014). With this in mind, the gatekeepers selected for the studies in this thesis were all individuals who had direct contact with potential participants either in a professional work manner or as part of their health care team. As the studies in this thesis look to recruit in multiple care sites across the seven health boards in Wales, gatekeepers were seen as a necessary and valuable resource in ensuring the research sample could be obtained. The specific ways that gatekeepers were involved will be outlined in the individual study chapters (see chapters 4,5,6).

### 3.3.6.3 Determining sample sizes

When determining sample sizes, the concept of data saturation was first introduced by Glaser and Strauss in 1967 and is defined as “*the point in data collection and analysis where new information produces little or no change*” to the codes created (Guest *et al.*, 2006 pg.65). Data saturation has historically been used in qualitative research to determine sample sizes and improve validity in results. However, O’Reily and Parker (2013) argue that as qualitative research and methods progress, the use of data saturation may not be suitable anymore, highlighting that different qualitative methods of data collection and analysis have different requirements in terms of the quantity of data needed. For example, studies using Interpretative Phenomenological Analysis (IPA) typically have very small sample sizes (Smith 2015), in these cases data saturation most likely has not been achieved, but the results still provide extremely valuable and rich data.

Malterud *et al.*, (2016) suggests that instead, a concept called ‘information power’ should be used to help determine sample sizes in qualitative research and have created a model to assist in doing this. The model takes different factors about the individual research study into consideration and suggests that these factors all have an impact on the required sample size. The factors considered include the aim of the study, the specificity of the sample, the use of theory, the quality of the dialogue and the type of analysis chosen. Information power has been used in a number of studies such as Soklaridis *et al* (2017), who looked at the experiences of female CEOs and Walseth *et al* (2017), who looked at partner relationships and how obsessive-compulsive disorder affects this. In these studies, information power seems to provide a method of being able to determine a general sample size needed for qualitative studies using a range of analytic methods. The researcher used information power to estimate sample sizes for studies 2 and 3. By considering the aims of the research, the specificity of the sample and the type of analysis planned, sample sizes were estimated for studies 2 and 3. As the thesis aimed to improve the overall patient experience, it was estimated that a larger sample of patients (7-15 participants) would be needed from each of the seven health boards in study 2 to gain valuable data across Wales compared to the estimated number of prescribers needed (5-7 participants) in study 3. As issues are often seen when prescriptions for unlicensed ‘special’ medicines are transferred between care settings, a larger sample of primary care prescribers were required in study 3. It was estimated that 5-7 prescribers from each of the seven health boards would be required to produce valuable data (3-5 from primary care and 1-2 from secondary care). Information power was not used to estimate a sample size in study 1 as a census was taken.

However, Sim *et al* (2018) argues that while giving an estimation of sample size may be a crucial part of designing a research study, it can be challenging when conducting inductive

research such as the studies in this thesis, and that the process of determining the sample size should be reflected upon and judged by the researcher throughout the research process. With this in mind, the researcher had a reflexive approach towards the sample size and was open to the number of participants changing once data collection had begun. Sample size estimations using the concept of information power will be provided in each individual study chapter (see chapters 4,5,6).

### **3.3.7 Qualitative data analysis**

As described above, (see 3.3) qualitative data consists of words rather than numbers, and can be collected in a range of forms, for example observational notes or transcribed interviews, however the researcher is responsible for interpreting the data to effectively explain what the information means (Pope 2000). The key difference between qualitative and quantitative analysis is that qualitative results are not measured but interpreted, and as such, statistical analysis approaches are not suitable.

Coding the data is an important aspect of qualitative analysis, this is where researchers read through the data gained and assign labels to the topics identified to summarize what had been said, these labels are called codes (Linneberg and Korsgaard 2019). Coding in this way allows the data to be categorised into the patterns identified, to collate the evidence and understand its meaning (Patton 2002 as cited in Wong 2008). Qualitative data is typically analysed using deductive or inductive approaches. Deductive analysis involves having some initial codes created before reviewing the data, these initial codes could be created using evidence already gained within the existing literature, or based on theory (Bradley, Curry and Devers, 2007). As the aim of the study was to gain the views and experiences of the participants involved, it was determined that a deductive approach would not be as suitable for the analysis as a more inductive, data-driven approach. Inductive analysis is data-driven and involves creating codes directly related to the data gained and does not require a coding frame to be created prior to reviewing the data (Braun and Clarke 2006). In this way the themes constructed are only related to the data gained and not previous evidence or theories. This was determined to be the most suitable analysis method to address the research aim of exploring the views and experiences of the individual participants.

Qualitative analysis is a complex field with some concepts relating to methodological approaches and methods of analysis, and some concepts encapsulating a range of analysis methods. For example, thematic analysis can be an individual analytic method such as reflexive thematic analysis (Braun and Clarke 2019) or can be considered an overarching term, which includes a range of analytic methods (Lester, Cho and Lochmiller 2020). Individual qualitative analysis methods can be associated with specific theoretical

perspectives, for example grounded theory analysis and interpretative phenomenological analysis or can be used across research paradigms such as reflexive thematic analysis (Braun and Clarke 2020).

### **3.3.7.1 Grounded theory analysis**

Grounded theory (see 3.3.2) is not only a methodological approach used to explore topics, but also an analytic method (Chong 2019). As such, aims to create a theory based on the data gained (Punch 2013). A simplified version of the main stages involved in grounded theory analysis is: (1) in-depth coding; (2) shorter code phrases; (3) grouping of codes; (4) creation of subcategories; (5) linking categories; and (6) creation of the core category (Eaves 2001). As grounded theory was determined not to be a suitable approach to address the research aims of the thesis, the analysis method was also deemed not suitable as the researcher was not attempting to develop theories based on the evidence gained.

### **3.3.7.2 Interpretative phenomenological analysis (IPA)**

Interpretative phenomenological analysis is associated with the phenomenological approach and provides in-depth examinations of qualitative data for each participant before highlighting the patterns between them (Eatough and Smith 2017). Analysis involves a detailed exploration of each participants' accounts, be this one single participant in a case study or multiple participants where patterns within the data are highlighted (Smith 2011). The different stages involved during IPA include: (1) looking for themes; (2) connecting the themes; (3) continuing analysis with other cases; and (4) writing up (Smith and Osborn 2007). This would have been a suitable approach to meet the aims of the research aim as the researcher took a phenomenological approach however, as the researcher was planning to obtain relatively large sample sizes this method of analysis would not be practical.

### **3.3.7.3 Thematic analysis**

Thematic analysis is used to identify patterns within the qualitative data gained, which are then constructed into themes, it aims to interpret the findings rather than summarising the information gained (Maguire and Delahunt 2017). As described above, thematic analysis is an overarching term for a range of thematic analysis techniques for example, reflexive thematic analysis and framework analysis.

#### **3.3.7.3.1 Framework analysis**

Framework analysis involves the creation of a thematic framework that the researcher then uses to analyse the data. The themes within the framework can be created prior to analysis and further themes identified in the data can be added (Setia, 2017) and therefore uses deductive and inductive approaches. There are 5 key steps to conducting framework analysis; "(1) *data familiarization*; (2) *identifying a thematic framework*; (3) *indexing all study*

*data against the framework; (4) charting to summarize the indexed data; and (5) mapping and interpretation of patterns found within the charts”* (Ritchie and Spencer 1994, as cited in Goldsmith 2021 pg.2062). As the aims of the research were to solely explore the views and experiences of the participants, the researcher decided this method of analysis would not be the most suitable as the themes created were not aimed to be related to previous evidence or theories and rather be completely data-driven.

#### **3.3.7.3.2 Reflexive thematic analysis**

Reflexive thematic analysis uses an inductive approach which emphasises the reflexivity of the researcher, the method is not associated with any theoretical perspective and therefore can be used across a range of qualitative studies (Terry and Hayfield 2020). Conducting reflexive analysis involves six key stages: (1) data familiarisation; (2) creating initial codes; (3) searching for themes; (4) reviewing themes; (5) defining the themes; and (6) writing the report (Braun and Clarke 2006). As this method offered an approach to create data-driven results it was deemed the most suitable approach (see chapter 4.4.7 for a more in-depth explanation of the steps taken when conducting reflexive thematic analysis).

#### **3.3.8 Purpose of the research**

The specific methods selected, and how they will be integrated depends on the purpose of the research. Greene, Caracelli and Graham (1989) suggest five reasons for conducting mixed method research: triangulation, complementarity, development, initiation, and expansion. The use of mixed method phenomenological research has been seen to increase over the years as researchers consider multiple perspectives to get a wider understanding of the topic being studied (Mayoh and Onwuegbuzie, 2014). As the studies in this thesis aimed to gain detailed qualitative views and experiences, quantitative methods could be used to complement the qualitative findings of individual studies in different ways.

Overall, as this research aimed to explore the views and experiences of participants across care settings in multiple roles, and to get a better understanding of the supply chain of unlicensed ‘special’ medicines across the healthcare system, a primarily qualitative phenomenological approach was deemed to be most appropriate. Any quantitative methods that were adopted in this thesis will be outlined in the individual study chapter (see chapter 5).

### **3.4 Researcher characteristics and reflexivity**

The researcher did not personally, and did not know anyone personally, who had a prescription for an unlicensed ‘special’ medicine, during the study and had never met the



participants prior to the interviews being conducted. This meant the researcher had no bias in terms of the responses and only had assumptions based on previous anecdotal evidence suggested by pharmacists, stakeholders, and evidence from the limited amount of previous research. This allowed the researcher to be open to each participant's individual experiences and feelings and led to the themes constructed during analysis to be completely data driven.

The researcher had previous experience talking to members of the public about sensitive topics. This included discussing health and mental health in a supportive role, as well as previous experience conducting research interviews aimed at exploring and discussing life threatening medical conditions. The researcher was therefore seen as capable of creating rapport and good relationships with the participants and being able to discuss potentially sensitive topics with care and respect.

As the study primarily consisted of qualitative methods, a reflexive approach was taken during the entire research process. Reflexivity has been described as "*the heartbeat of qualitative inquiry*" (Lindlof and Taylor 2017 pg.113). It requires the researcher to acknowledge the impact the research process has on them personally, as well as the changes they experience (Palaganas *et al.*, 2017), and to be able to critically reflect on how these factors and the researcher's own perspectives, could impact the research and results (Guillemin and Gillam 2004; Jootun *et al.*, 2009). Watt (2007) suggests that reflexivity is an extremely useful skill and can improve a researcher's work, by reflecting on their own actions and thoughts as well as the subject matter being studied, it allows researchers to be more receptive of challenges and their own influences and can help to create new insights or research questions (England 1994). These factors were all important as the nature of qualitative research methods means the researcher's abilities and personal opinions are more likely to influence the research and therefore the quality of the results (Anderson 2010). The researcher made notes throughout the research process and directly after every interview conducted in order to reflect on the impressions of the interview and also used the transcripts to reflect on their own skills in the hopes of improving the interview technique. Reflexive discussions will be provided across the thesis, explaining how the reflexive approach was used throughout the research process and providing personal reflections on the research experience as a whole.

### **3.4.1 Building an understanding**

As the researcher did not have a background in pharmacy, they began by reviewing the guidance and literature around the use of unlicensed 'special' medicines and visiting some community pharmacies, a specials manufacturing unit, and having multiple discussions with clinicians and key stakeholders. When concepts arose during data collection that the

researcher was not familiar with, this was discussed with the project supervisors and resources to improve knowledge in these areas were provided. This allowed the researcher to gain an understanding of what unlicensed 'special' medicines are, when and how they are used within the UK, and some of the issues that had been previously identified in the literature or experienced by stakeholders. The researcher continued reviewing literature throughout the research process in order to maintain awareness and understanding around the topic and to stay up to date with new available literature.

### **3.5 Techniques to enhance trustworthiness**

Qualitative research has some general limitations - data collection, transcription and analysis can be time consuming (Choy 2014), and the results gained may not be representative of the target population as each individual may have differing experiences (Atieno 2009). Lincoln and Guba (1985) suggest four key aspects when determining trustworthiness in qualitative research: credibility, transferability, dependability, and confirmability. These concepts were suggested to replace the commonly used concepts when determining trustworthiness in quantitative research: internal validity, external validity, reliability, and objectivity, respectively (Lincoln and Guba 1982). A description of the methods or techniques used to address these aspects is provided below.

#### **3.5.1 Credibility**

In order to be seen as credible, the findings of the research should be a true representation of the topic being explored (Shenton 2004). Multiple strategies including prolonged engagement and triangulation have been suggested to increase the credibility of the findings (Lincoln and Guba 1986). The researcher took steps to increase the credibility of the research by taking time towards the start of the research process to visit and engage with professionals at community pharmacies, a specials manufacturing unit and shadowed a secondary clinician in order to familiarise themselves with the overall supply chain of unlicensed 'special' medicines and gain a range of perspectives from those involved. Data triangulation, where results are compared for different sample populations (Hussain 2009) with integration taking place after each data set had been analysed was also planned to take place, this involved arranging a meeting with a Stakeholder Steering Group (SSG) to help contextualise the results (see chapter 7).

#### **3.5.2 Transferability**

As the studies in the thesis look to explore individual perceptions and experiences, the results gained may not be generalisable to other settings and may not even be

representative of the population as a whole. However, thick descriptions of participants responses have been suggested as a method of increasing transferability (Schwandt Lincoln and Guba 2007), along with a description of the context of the research, how the participants were selected, their characteristics, and how methods were used to collect and analyse the data (Graneheim and Lundman 2004). The thesis will provide all of the above, starting with the context of the research, followed by a detailed description of the methods involved, along with how they were used throughout the research process and finally by providing detailed verbatim quotes in the results sections. Examples of coded interview transcript pages can also be seen in Appendix 4.

### **3.5.3 Dependability**

Guba and Lincoln (1989) suggest that decisions made throughout the qualitative research process can lead to changes in the methods or findings and that the researcher should allow these decisions and the effect they had on the research to be reviewed in a dependability audit. Multiple authors have suggested the use of an audit trail as a means of increasing dependability of a study (Tobin and Begley 2004; Yilmaz 2013) and as suggested, the researcher has outlined in detail decisions about the research approaches and methods selected and will provide evidence directly from the data gained so that the process and results can be examined. The researcher chose to use peer examination and the code-recode strategy as described by Anney (2014) to increase the dependability of the research. This involved coding and recoding the transcripts two weeks apart and comparing the codes created and discussing the research methods and findings with peers.

### **3.5.4 Confirmability**

For results to be viewed as confirmable, it must be clear they have been derived from the results gained and not a representation of the researcher's own perspective and views (Korstjens and Moser 2018). In order to achieve this, the researcher took steps to ensure the research methods and findings were transparent. Transparency is an important aspect of qualitative research, without being able to review the methodology, process and data of a study, other researchers would not be able to confirm or trust the results and implications of the study and would be less inclined to continue further research in that area (Moravcisk 2014) resulting in potentially meaningful data to be lost. Good transparency in research allows for easy replication of studies which can strengthen results or improve the reliability of the results over time. In an effort to increase rigour, transparency and replicability, the structure of the thesis was based on the standards for reporting qualitative research (SRQR) suggested by O'Brien *et al* (2014). The suggested structure includes 21 points to address

which leads to a detailed account of the design, timescales, methods, and procedures of the studies to be produced.

### **3.6 Engagement with stakeholders**

Engagement with stakeholders throughout the research process has been reported in many studies. A systematic review revealed that 36% of researchers who engaged with stakeholders reported shared decision making and 20% reported an improvement in the relevance of the research (Concannon *et al.*, 2014). Other studies have suggested that when engaging with stakeholders, the quality of the research can be improved by gaining the key perspectives and understandings of those directly involved in different aspects of the topics being studied (Esmail, Moore and Rein 2015). With this in mind, it was sought to establish a SSG for this research.

The researcher proactively identified key sectors from which members needed to be sought, and in collaboration with supervisors and funders, individuals were approached. The seven members of resulting SSG included professionals in a range of roles, specifically a member on the board of Community Pharmacy Wales (CPW), members from a 'specials' manufacturing unit, members of the Primary, Community and Intermediate Care (PCIC) clinical board, an All Wales Medicines Procurement Specialist Pharmacist and a superintendent of a chain of community pharmacies in Wales. Engagement with the SSG was sought throughout all aspects of the research development and implementation, as detailed below.

#### **3.6.1 Design of methodology**

SSG members took part in reviewing and providing feedback on study documents and approaches to accessing selected population groups. The feedback gained from the steering group helped the researcher to develop the overall protocol and study documents and allowed the researcher to better tailor the approaches to accessing participants within the NHS and community pharmacies. A description of the SSG impact on the study documents will be outlined in the individual study chapters (see chapter 4,5,6).

The researcher also spent some time at a local hospital and gained patient involvement by showing patients waiting to be seen a copy of the patient information booklet to gain their feedback. The responses were helpful and supported the acceptability and readability of the booklet from the patient perspective.

### **3.6.2 Recruitment**

One member of the SSG was the head of a small chain of community pharmacies and agreed to act as a gatekeeper to help recruit participants into study 1. Another member of the steering group is a member of CPW who also agreed to act as a gatekeeper and helped the researcher to contact and aid recruitment in study 2 by contacting selected community pharmacies to see if they would have capacity to get involved and supply information to patients.

### **3.6.3 Contextualising results**

Members of the SSG also helped to contextualise results within different aspects of the healthcare system, allowing the researcher to gain insights and perspectives across care settings and to better understand the practical implications of the research findings or of the recommendations created as a result of the findings.

### **3.6.4 Wider dissemination**

The SSG members helped to disseminate the findings of the research by reviewing and co-authoring a paper on the results of study 1.

The researcher ensured continuous engagement by maintaining consistent regular contact with the SSG, newsletters were created periodically (see Appendix 5) and face to face or virtual meetings were held quarterly (when practical).

## **3.7 Ethical and regulatory considerations**

All studies were carried out in accordance with the Research Integrity and Governance Code of Practice, laid out by Cardiff University.

### **3.7.1 Informed consent**

Only subjects able to give informed consent were invited to take part in the study and participation was voluntary. All participants were given an information sheet to read prior to deciding whether to take part in the study and were given the opportunity to contact the researchers with questions. They were asked to sign a consent form (see Appendix 6), were informed of their right to withdraw at any point during the investigation and were assured that their data would be removed if they requested so until the point of complete anonymisation. After this point individual participant's data could not have been removed as there would have been no way to identify the transcript with the participant.

### **3.7.2 Confidentiality**

All participants were anonymised and were given interview/participant numbers in the final report, all audio recordings of interviews and any identifiable data was deleted immediately after transcription. All information was kept strictly confidential by the researcher. At no point did the researcher have access to patient medical records and patients' medical treatment was not impacted in any way as the result of the research. All consent forms would be kept in a locked secure location at Cardiff University for 15 years in accordance with the Data Protection Act 2018 and the record retention policy of Cardiff University.

### **3.7.3 Anonymisation**

Complete anonymisation occurred once the interviews had been transcribed. The researcher deleted the audio recordings made along with any identifiable data, at this point there was no way to connect individual comments made with individual participants.

### **3.7.4 Peer review**

The project was a funded student project going towards a PhD qualification. The outline of the study was reviewed by KESS 2 and the overall project including protocol and study documents were created by the student researcher and reviewed by the project supervisor.

### **3.7.5 Ethical approval**

As all the studies involved qualitative interviews discussing the service and treatment provided or received it was deemed that there was a minimal risk to participants.

#### **3.7.5.1 Study 1**

Before the start of recruitment, a favourable opinion was sought from Cardiff University, specifically from Cardiff School of Pharmacy and Pharmaceutical Sciences and this was granted on the 9<sup>th</sup> of August 2018 and given the reference number 17-18 28. This approval allowed recruitment to begin with the pharmacists and pharmacy technician sample population. Sponsorship was sought from Cardiff University and this was granted on the 30<sup>th</sup> October 2018.

#### **3.7.5.2 Study 2 and 3**

Since the project was extended to incorporate studies 2 and 3, further approvals were sought. The additional studies were reviewed and gained sponsorship from Cardiff University on 6<sup>th</sup> August 2019. As the study involved human participants approvals were sought from the NHS using the Integrated Research Application System (IRAS) which is then passed to a research ethics committee and the Health Research Authority (HRA). The

IRAS application, which included a 125-page protocol containing supporting documents, was submitted on 23<sup>rd</sup> August 2019, and given the IRAS ID: 268899. Aneurin Bevan health board was the central site for this study. A favourable opinion was granted by the North West - Liverpool Central Research Ethics Committee and given the reference number (19/NW/0598) and full HRA/NHS approvals were gained on the 20<sup>th</sup> January 2020. A timeline of the ethical approval process for studies 2 and 3, along with amendments submitted can be found in table 3.1. Due to the Covid-19 pandemic, the resulting impact on NHS services and the restrictions put in place across Wales, all research activity was postponed for around five months. A description of the impact the Covid-19 pandemic had on the research process can be seen in studies 2 and 3 and some reflections on conducting research during the Covid-19 pandemic are provided in Appendix 7.

**Table 3.1** *Timeline of the ethical approval process*

**Ethical approval process, University, IRAS, REC, HRA and HCRW**

<b>Feb 2019 -</b>	<i>MPhil officially converted to PhD.</i>
<b>Feb - July 2019 -</b>	<i>Created larger project suitable for PhD with supervisors, drafted protocol, created draft interview schedules, gained feedback from multiple meetings with steering group members, key stakeholders and patients, reviewed and edited protocol and study documents.</i>
<b>June 2019 -</b>	Began IRAS online application process.
<b>June – July 2019 -</b>	Multiple meetings held with Aneurin Bevan research facilitator to assist in understanding the research application process.
<b>12<sup>th</sup> July -</b>	Finalised protocol and all study documents and sent to Research governance team for University sponsorship.
<b>6<sup>th</sup> August 2019 -</b>	Letter of sponsorship gained from Cardiff University.
<b>23<sup>rd</sup> August 2019 -</b>	Completed supporting documents for and Submitted full IRAS application – 125-page application pack.
<b>4<sup>th</sup> Sep 2019 -</b>	The Research Ethics Committee issued a Favourable Opinion with additional conditions with comments to be addressed.
<b>25<sup>th</sup> Sep 2019 -</b>	Comments reviewed, study documents edited and uploaded to IRAS and re-submitted for review.
<b>21<sup>st</sup> Oct 2019 -</b>	HCRW portfolio team requested sponsor declaration and application.
<b>22<sup>nd</sup> Oct 2019 -</b>	Research governance team said declaration would be sent.
<b>25<sup>th</sup> Nov 2019 -</b>	<b><i>Delay experienced</i></b> - Declaration received from research governance team after prompt (miscommunication - we had thought the team would send directly to the research portfolio co-ordinator as last messaged received said “I will send out the declaration later today”

## Ethical approval process, University, IRAS, REC, HRA and HCRW

- but they had just forgotten to send it out to us on the 22<sup>nd</sup> Oct).  
Declaration sent to portfolio co-ordinator the same day.
- 26<sup>th</sup> Nov 2019 -** The Research ethics committee approved that the additional conditions had been met and supplied further information required for full HRA/HCRW assessment.
- Comments reviewed and response returned.
- 23<sup>rd</sup> Dec 2019 -** ***Delay experienced*** - Contacted by HRA and asked for response already provided above, email forwarded to show previous response had been sent.
- HRA and Health and Care Research Wales (HCRW) Approval Letter gained.**
- Dec-Jan 2019-20**  
- Created research passport applications and localised information packs for each health board.
- 28<sup>th</sup> Jan 2020 -** Localised information packs and Organisation Information Documents approved by Research governance team.
- Jan-Feb 2020 -** ***Delay experienced*** - Amendments made, documents edited and submitted. previous delay resulted in inactive work phone number being reassigned – unforeseen event.
- 5<sup>th</sup> Feb 2020 -** Study determined eligible and assigned to the Central Portfolio Management System (CPMS).
- 6<sup>th</sup> Feb 2020 -** Gained 'Introduction to Good clinical practice (GCP) eLearning' certification from The National Institute for Health Research (NIHR) (as requested from Aneurin Bevan research facilitator). Sent out to all health boards.
- 12<sup>th</sup> Feb -** Research passports approved by University registry.
- Feb 2020 -** Sent out approved local information packs and research passport applications to each health board.
- 13<sup>th</sup> Feb 2020 -** **Letter of access gained from Aneurin Bevan University health board.**
- 19<sup>th</sup> Feb 2020 -** Amendment approved and sent to all health boards.
- 21<sup>st</sup> Feb 2020 -** Gained EIDO Healthcare *be* INFOrMED online consent training certification (as requested by Cardiff and Vale research facilitator). Sent out to health boards.
- 24<sup>th</sup> Feb 2020 -** **Letter of access received from Hywel Dda University health board.**
- Feb -March 2020**  
- **Official recruitment began** - Accessed GP lists from approved health boards, began contact with 3 GP surgeries about potential



### Ethical approval process, University, IRAS, REC, HRA and HCRW

recruitment, study documents sent to one surgery awaiting response from others (before lockdown).

Alesha and CPW contact began process of community pharmacy selection and access in approved health boards.

- 11<sup>th</sup> March 2020** - Dermatology meeting attended, research introduced, and potential participants and gatekeepers were invited to participate.
- Steering group meeting held– decision made to **postpone recruitment of patients** due to the increasing spread of Covid-19.
- 16<sup>th</sup> March 2020** - Informed that Aneurin Bevan had postponed all non-essential research due to COVID-19. **Full recruitment postponed.**
- 20<sup>th</sup> March 2020** - HCRW release statement “Until further notice, Health and Care Research Wales through its services is pausing the site set up of any new or ongoing studies at NHS and social care sites that are non COVID-19 studies.”
- 30<sup>th</sup> March 2020** - **Letter of access gained from Cwm Taf Morgannwg University health board.**
- 30<sup>th</sup> April 2020** - **Letter of access gained from Powys teaching hospital.**
- 09<sup>th</sup> July 2020** - Amendment submitted to manage impact of COVID-19 on obtaining consent virtually.
- August 2020** - **Recruitment re-started in selected health boards.**
- 30<sup>th</sup> August 2020** - Amendment submitted for Cardiff and Vale University Health Board to agree on local collaborators
- 14<sup>th</sup> Oct 2020** - **Letter of access gained from Cardiff and Vale University health board.**
- 13<sup>TH</sup> Jan 2021** - Amendment submitted to extend the project period.
- 10<sup>th</sup> Feb 2021** - **Letter of access gained from Swansea Bay University health board.**

## 3.8 Summary

Overall, the researcher chose an interpretivist research paradigm with a phenomenological approach and a primarily qualitative design. Quantitative methods were selected to compliment the qualitative research aims in one study, the individual designs and specific methods chosen for each study will be outlined in the upcoming individual study chapters (see chapters 4,5,6). The researcher chose to take a reflexive approach throughout the

entire research process and has taken steps to increase the trustworthiness of the research as a whole, such as explaining decisions made when designing the research, and providing detailed accounts of the methods used.

## **4. Study 1 – Semi-structured interviews with community pharmacy staff**

### **4.1 Overview of chapter**

This chapter contains a brief introduction to the study, which will outline the justification for conducting the research along with the study specific aims and objectives. This will be followed by a description of the specific methods used to explore the views and experiences of community pharmacists and community pharmacy technicians around the use of unlicensed ‘special’ medicines in Wales. Steps taken to gain ethical review and approval will also be outlined.

A detailed description of the sampling and recruitment processes will be provided including the eligibility criteria used, and an outline of the role the gatekeeper had in facilitating access to potential participants. Following this, the data collection and analysis methods will be outlined along with the ethical considerations pertaining to participants.

The results of the semi-structured interviews conducted will be provided, starting with descriptive information about the sample gained, and a detailed look at the results of the analysis. Each theme constructed through reflexive thematic analysis will be explained in detail and quotes will be used directly from the interview transcripts to support the findings.

Lastly, a discussion of the main findings will be provided within the context of the existing literature along with the study limitations, reflective notes and overall conclusions. The results from this chapter have been written up and published by the researcher in the *Integrated Pharmacy Research and Practice* journal, an international peer-reviewed, online journal (Wale *et al.*, 2020).

### **4.2 Introduction**

Community pharmacy staff play a vital role in the supply of prescription medicines including unlicensed ‘special’ medicines, as they are the first point of contact for patients in the community. Over time the role of the community pharmacist has evolved from simply checking and dispensing medicines to a more patient-focussed role, involving disease management (George *et al.*, 2010) providing health care advice, and liaising with members of the interdisciplinary team to refer patients when appropriate (Taylor and Harding 1989) (see chapter 1.5.2). Many community pharmacists have also taken part in running successful interventions, for example smoking cessation services (Sinclair, Bond and Stead 2004; Peletidi, Nabhani-Gebara and Kayyali 2016).

The introduction and systematic review chapters (see chapters 1 and 2) highlight the issues faced when trying to access unlicensed 'special' medicine in the community. One difficulty for community pharmacy staff that has been reported in the UK was a lack of accessibility, with staff being unable to find a supplier or manufacturer for a certain product or specific formulation (Wong *et al.*, 2006; Husain, Davies and Tomlin 2017), although this was reported from the patient perspective. The available guidance and information created to support healthcare professionals when acquiring and supplying unlicensed 'special' medicines is limited by the lack of consistent definitions and terminology (Donovan *et al.*, 2018) and it has been suggested that this lack of consistency in terminology can lead to confusion for healthcare professionals (Aronson and Ferner 2017).

Despite there being over 700 community pharmacies across Wales (CPW 2021) and almost £4m spent on 'specials' in Wales alone between August 2015 - July 2016 (Mantzourani 2019), to the researcher's knowledge, there are no studies exploring community pharmacy staff views around the use of unlicensed 'special' medicines solely in Wales, where the responsibility for National Health Service (NHS) Wales lies within the Welsh Cabinet Secretary for Health and Social Service after devolution. A small chain of community pharmacies part-funded this part of the project, when the researcher was completing the first year as an MPhil qualification and before this was transferred to a PhD qualification and as such became the sample population for study 1. The chain of community pharmacies had experienced issues with the access and supply of unlicensed 'special' medicines in the past and were interested in conducting research to explore any ongoing challenges in this area.

In order to address the overall thesis aim of improving the patient experience, it was important to better understand the views and experiences of community pharmacy staff. This would enable issues currently being faced within community pharmacies when accessing and supplying unlicensed 'special' medicines to be identified, and evidence-based recommendations for change to be created.

#### **4.2.1 Study 1 aims and objectives**

The aim of study 1 was to explore the views and experiences of community pharmacy staff around accessing and supplying unlicensed 'special' medicines.

##### **Objectives:**

- To explore pharmacy staff understanding and awareness of the use of unlicensed 'special' medicines;
- To explore pharmacy staff perceptions of acceptability when obtaining and supplying unlicensed 'special' medicines;

- To explore pharmacy staff experiences related to the accessibility of unlicensed 'special' medicines;
- To explore pharmacy staff experiences when supplying unlicensed 'special' medicines.

### **4.3 Ethical approval process**

The project was funded by the Knowledge Economy Skills Scholarships (KESS 2), with contributions from a small chain of community pharmacies and an unlicensed 'special' medicines manufacturing unit. As this study did not involve recruiting NHS patients ethical approval from the NHS was not sought, instead the community pharmacy chain who part funded the project approved the research within their company. A favourable opinion was sought from Cardiff University's School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee and ethical approval was granted on the 9<sup>th</sup> of August 2018 and given the reference number 17-18 28 (see Appendix 8). For more details on ethical and regulatory considerations, see chapter 3.7.5.

### **4.4 Methods**

Due to the large number of unlicensed 'special' medicines available for a wide variety of conditions, it was expected that community pharmacy staff may have differing experiences and therefore a range of views and perceptions. In order to explore and better understand each participant's individual experience, a constructivist research paradigm with a qualitative phenomenological approach was selected (see chapter 3.2 and 3.3). In this way the individual participants' subjective reality could be explored and obtained.

To gain a better understanding of the views and experiences of community pharmacy staff, semi-structured interviews were chosen. It was highlighted in chapter 3 (see 3.3) that semi-structured interviews allow the researcher to gain in-depth information and ask about the different aspects involved in obtaining and supplying unlicensed 'special' medicines, while also allowing the participant to raise factors that are important to them. As this is an unresearched area of study, allowing the participants to raise issues not predetermined by the researcher was seen as an appropriate way to address the study aims.

#### **4.4.1 Data collection materials and technologies**

Community pharmacy staff comprises pharmacists, pharmacy technicians and dispensers. Pharmacists and pharmacy technicians both play a role in obtaining and supplying unlicensed 'special' medicines, with community pharmacists being responsible for judging the clinical suitability of the medicine for the patient (RPS 2015), and pharmacy technicians

who are responsible for preparing, dispensing and supplying medicines (PSNC 2022a). As such, the researcher aimed to explore the views of these two samples. The researcher firstly created a semi-structured interview schedule for pharmacists, which focussed on four main areas; the process, access, supply, and experiences related to working with unlicensed 'special' medicines in a community pharmacy (see Appendix 6). The questions aimed to get the participants to outline and describe the process that takes place when a prescription for an unlicensed 'special' medicine is received, along with questions aimed at understanding their views around their roles and their experiences. The interview schedule created for the pharmacists was then adapted to create an interview schedule for pharmacy technicians. This schedule also focussed on the process, access, supply and experiences related to working with specials in a community pharmacy (see Appendix 6). The interview schedules differed slightly as the two professions have different responsibilities within the pharmacy. The pharmacist interviews sought to explore the decision-making processes involved, and pharmacy technician interviews focussed more on their level of involvement. The creation of the interview schedule, study documents and protocol was an iterative process, whereby multiple cycles of feedback and improvements were undertaken, between the student and the supervisory team. Feedback was also sought from the SSG. Originally one interview schedule was created for community pharmacy staff, after discussions with the supervisory team it was determined that some of the questions would not be suitable for community pharmacy technicians who do not make the clinical decision to supply the medicines. As such, a more concise interview schedule was created for community pharmacy technicians. A steering group meeting was also arranged, and members were sent copies of the interview schedules and protocol to give further feedback on, this feedback was taken into consideration and the documents were updated accordingly. An example of an update made using feedback from the SSG was the inclusion of a question in the interview schedule for community pharmacists, to explore the use of any standard operating procedures (SOPs), something the researcher had not considered prior to the feedback provided.

Study documentation included a personalised email to the primary gatekeeper, an email invite to all pharmacists and pharmacy technicians, an information sheet, a consent form, an interview schedule for pharmacists and an interview schedule for pharmacy technicians. An audio recorder was used during data collection along with a notepad to make notes of any observational factors. A laptop and NVivo qualitative data analysis software (QSR International Pty Ltd. Version 12. 2018) were used during the initial transcription and analysis. All participants in this sample were supplied with the same documents and information.

## 4.4.2 Recruitment strategy

As study 1 was originally planned as part of an MPhil project, potential participants were limited to one small chain of community pharmacies in South Wales, which part funded the project. This included eight registered pharmacists and seven registered pharmacy technicians working at the chain of community pharmacies in South Wales at the time. A census of all potential participants who had a minimum of 1-year experience working in a community pharmacy, so as to increase the likelihood that they would have had some experience with obtaining or supplying unlicensed ‘special’ medicines. All participants were presumed to be aged 18+ and able to give informed consent due to their profession, and in the case of pharmacists, registration with the General Pharmaceutical Council, the regulatory body of pharmacy professionals in the UK.

One pharmacist (who was identified prior to the start of the study), agreed to act as a primary gatekeeper in recruiting the other pharmacists and pharmacy technicians. The primary gatekeeper was sent a personalised email invitation containing all relevant study information and was asked to forward this information by email to all other pharmacists and pharmacy technicians who fit the eligibility criteria (see table 4.1). The participants then contacted the researcher directly to arrange a suitable time for the interview or contacted the gatekeeper and gave them permission to pass along their information to the researcher. The email with study information was re-sent to all potential participants as a reminder to those who had not contacted the researcher after two weeks, and again after one month. Participants who had responded previously were asked to ignore the reminder emails and if any potential participants had not responded after this point, it was assumed they did not wish to take part and no further contact was made by the gatekeeper to recruit participants. Recruitment took place from September 2018 and continued until January 2019.

**Table 4.1** Inclusion and exclusion criteria for participants in study 1

Eligibility criteria	Pharmacists and pharmacy technicians
<b>Inclusion Criteria</b>	
Population	<ul style="list-style-type: none"> <li>Registered Pharmacists or pharmacy technicians currently working at the selected chain of community pharmacies;</li> <li>Assumed over the age of 18 due to their profession.</li> </ul>
Experience	<ul style="list-style-type: none"> <li>Experience (<math>\geq 1</math> year) procuring and dispensing unlicensed medication in a community pharmacy.</li> </ul>
Communication	<ul style="list-style-type: none"> <li>Can communicate effectively in English (does not have to be first language);</li> <li>Assumed capable of giving informed consent due to their profession and, in the case of pharmacists, annual declarations to the General Pharmaceutical Council (GPhC).</li> </ul>
<b>Exclusion Criteria</b>	
Experience	<ul style="list-style-type: none"> <li>Less than one year working in a community pharmacy.</li> </ul>
Communication	<ul style="list-style-type: none"> <li>Does not speak English.</li> </ul>

### **4.4.3 Setting**

Pharmacists and pharmacy technicians were interviewed in the consultation room at the pharmacy sites where they worked, which ensured recordings could be made in a quiet setting with minimal interruption. This could have had a negative impact on recruitment as other staff members may become aware when a participant was taking part. However, conducting the interviews in the pharmacy allowed all willing members of the sampling frame to have their interview in a comfortable familiar setting while minimising disruption and without needing participants to take time off work to participate, potentially improving the chances of maximising recruitment.

### **4.4.4 Ethical issues pertaining to subjects**

There were no perceived risks to the participants in this sample. As the researcher was working alone, lone worker issues were taken into consideration. To minimise this risk all interviews were arranged to take place in the community pharmacies during working hours and therefore were held in a public location. The researcher also informed the academic project supervisor of interview dates and times in advance by email.

### **4.4.5 Data collection**

Data was collected using semi-structured interview schedules. Once the researcher had received consent, a suitable time to go to the pharmacy and conduct the interview was arranged directly with the participant. Participants were given the opportunity to ask questions before and after taking part in the interview and notes were made by the researcher of any visual responses presented by the subjects, such as exaggerated facial expressions. All interviews were conducted face to face and recorded with a dictaphone to allow the researcher to pay complete attention to the participant and ensured a detailed transcript was created verbatim. Data was collected from September 2018 to the end of January 2019.

### **4.4.6 Data processing**

Audio recordings of data collected via semi-structured interviews were used to transcribe verbatim. Transcription involved using MS Word to get the initial information transcribed, the researcher then reviewed the transcription while listening to the audio tapes to confirm that it was correct and added any missing details or observational factors noted. As a reflective approach was used, the researcher used the transcriptions during data collection to review and improve the interview technique.



Once an individual transcription had been completed, the participant was given an interview/participant number for the analysis and report. The researcher deleted the audio recordings directly after transcription and in this way assured that complete anonymisation had been achieved. Transcripts were then uploaded to NVivo, a qualitative data analysis software, where analysis would be conducted. At this point, participants were no longer able to withdraw their data as there was no way to link the transcriptions to the individual participant.

#### **4.4.7 Data analysis**

Reflexive thematic analysis with an inductive approach was used to analyse the transcripts, the method suggested by Braun and Clarke (2006) was followed, which included six phases. The first phase was to process the data, and to read the transcripts multiple times in order to be familiar with the data. The second phase involved working through the whole data set and creating initial codes, which reflect the topics raised by the participants and could be specific or broad. The third phase involved turning and arranging these codes into themes and subthemes, this gave structure to the results and highlighted key areas addressed by the participants. The fourth phase was to review these themes both in terms of the extracts used, and to review the theme validity for the complete data set. The fifth phase required all themes and sub-themes to be clearly defined, and the sixth phase was writing the report.

Along with the techniques used to enhance trustworthiness as described in chapter 3 (see chapter 3.5), in order to increase rigour in the analysis, the researcher followed as many of the recommendations laid out by Castleberry and Nolen (2018) as possible. This involved conversing with other researchers who had experience using qualitative methods (mainly the academic supervisor), reflecting on and reporting any personal biases, and by using reliable research methods to answer the research questions. When it came to the actual analysis, this included taking time when coding and analysing the data, accepting the need to code and recode if necessary, and using quotes directly from the transcripts to support and provide evidence for the themes created. By being transparent with the methods and procedures used during the whole research process and showing this in the report, the researcher hoped to effectively represent their own experiences and the stages involved during the research process with the aim of producing a reliable, rigorous and replicable report.

## 4.5 Results

### 4.5.1 Participant characteristics

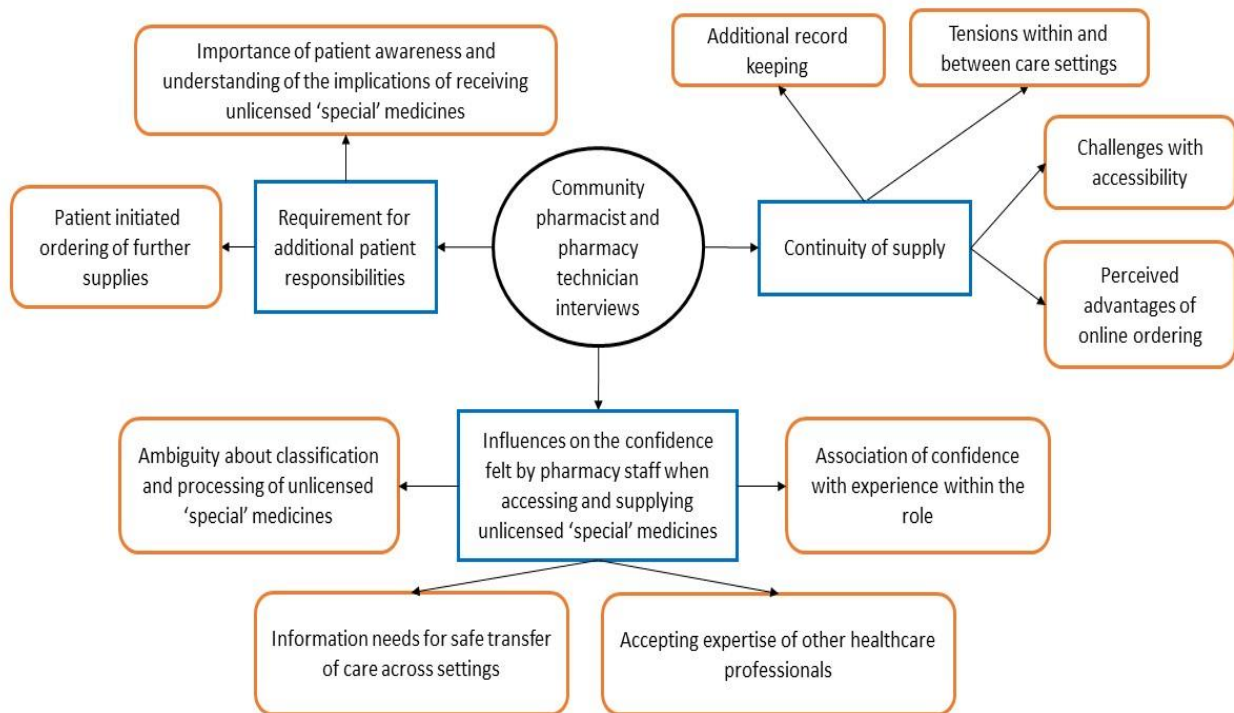
A total of 15 potential participants were invited to take part in the study, this included eight registered community pharmacists and seven registered pharmacy technicians. Of these, a total of six participants agreed and took part in the interview (n=5 pharmacists and n=1 pharmacy technician), giving a response rate of 40%. The semi-structured interviews conducted lasted between 20-40 minutes for pharmacists and 10-20 minutes for pharmacy technicians. The interview number given to each participant, their work experience, and the average number of unlicensed 'special' medicines dispensed per month can be seen in table 4.2. In an attempt to reduce the risk of compromising confidentiality due to the small sampling frame, participants' specific job role, age and gender are not specified.

**Table 4.2** Study 1 participant demographics and monthly average of unlicensed medicines dispensed in each pharmacy

Interview/participant number	No of years working as a registered pharmacist or pharmacy technician in a community pharmacy (yrs)	No. of Unlicensed 'special' medicines dispensed from the pharmacy on average, per month
INT 1.1	≥20	8
INT 1.2	≥20	4-5
INT 1.3	5-10	4-5
INT 1.4	>1<2	5-8
INT 1.5	>1<2	4
INT 1.6	5-10	4-5

### 4.5.2 Thematic analysis results

Reflexive thematic analysis of transcribed interviews revealed three main themes: (1) requirement for additional patient responsibilities; (2) influences on the confidence felt by pharmacy staff when accessing and supplying unlicensed 'special' medicines; and (3) continuity of supply. A graphic representation of the themes and main subthemes can be found in figure 4.1. Examples of coded interview transcript pages can be found in Appendix 4.



**Figure 4.1** Themes and subthemes constructed through thematic analysis of semi-structured interviews with community pharmacy staff

#### 4.5.2.1 Theme 1 – Requirement for additional patient responsibilities

Participants described how patients receiving unlicensed ‘special’ medicines were required to hold additional responsibilities compared to patients receiving licensed medications. Patient awareness and understanding of the challenges associated with obtaining and supplying unlicensed ‘special’ medicines was perceived as vital in ensuring the patient successfully took on these additional responsibilities, and strategies used such as communication tools to improve patient outcomes were highlighted.

##### 4.5.2.1.1 Importance of patient awareness and understanding of the implications of receiving unlicensed ‘special’ medicines

Patient awareness of the implications of receiving unlicensed ‘special’ medicines and how this differs to receiving licensed medicines, such as the extended lead times, was identified as essential in ensuring the patients could manage the timelines involved with accessing a ‘special’ in the community.

*“[Patients need] an understanding that [unlicensed ‘special’ medicines are] not something that we can just take off the shelf, that, we need a little bit of warning, that we can’t order it in advance without having the prescription...and they need to allow us enough lead time” [INT 1.2].*

However, participants reported varying levels of patient awareness when first attending the community pharmacy to receive their medicine. This included patient awareness around the fact that their medicine was classed as unlicensed, and also awareness of the differences in accessibility of unlicensed ‘special’ medicines.

*“[Patients are aware their medicine is unlicensed] once we’ve told them (laughs) you do get occasional, it tends to be the walk-in ones, and it’s the first time they’ve ever had it, and they’ll sort of come in and go ‘oh I’ll try somewhere else then’ and I’ll go ‘well you’re not going to get it anywhere actually’” [INT 1.2].*

Some patients were unaware of the differences in accessibility of unlicensed ‘special’ medicines and expected to receive the medicine the same day as handing in the prescription to the community pharmacy. Participants described how they perceived it to be part of their role to clearly explain the process and potential for delays when accessing unlicensed ‘special’ medicines that patients would need to be aware of. Participants outlined the balance of needing to inform patients about the use of unlicensed ‘special’ medicines while reassuring them in relation to potential risks.

*“I try not to bombard [patients] too much with, a lot of information about what has and hasn’t happened in the past, in terms of testing [for unlicensed ‘special’ medicines] because, you’ve got to get the balance between informing them of what’s going on, but also, not saying too much to kind of worry them and put them off taking it” [INT 1.4].*

This perceived balance resulted in less information being provided about what the unlicensed status meant and more information around how it would alter the typical process of accessing medicines from the community pharmacy. This balance was required as patients tend to have more concerns once they have been fully informed about using unlicensed ‘special’ medicines specifically when there may be limited clinical evidence available for that medicine.

*“Often patients are a little wary, you know because they realise that this is a special medication, and sometimes they will have talked with a consultant and they’ve been told that perhaps, it’s the first time it’s being used” [INT 1.1].*

One participant described how the concerns felt by the parents of patients about the use of unlicensed 'special' medicines were reported to impact the parents' perceptions of the treatment and their child's need. The participant described some parents feeling as though their child's treatment was experimental and questioning the need for the use of an unlicensed 'special' medicine.

*"One of the common discussions I will have [with parents is] well you know, 'is this really necessary?' and the other thing is 'is my child being used as an experiment?'" [INT 1.1].*

The participant addressed this situation by sharing their knowledge around the particular unlicensed 'special' medicine and the evidence and research available for the use of that product. The participant also described being honest about the choice and responsibility the patient has when deciding to take the medicine, or provide it to their child.

*"I say to them I can supply you with as much information as I can, you know, this is good, validated research, but at the end of the day, we're probably still learning, but your responsibility is, you've got to say whether you want to give it to your child, I can't go any further" [INT 1.1].*

Participants described how informing patients about what unlicensed 'special' medicines are and the resulting impact on accessibility, was seen as part of their role. The balance outlined by participants was perceived to be vital in ensuring that the patient was aware enough to manage the timelines involved, while not causing too much concern that it would impact their decision to adhere to taking the medicine.

#### **4.5.2.1.2 Patient initiated ordering of further supplies**

Participants reported relying on patients to inform them in advance of when further supplies of an unlicensed 'special' medicine would be needed. The participants outlined some of the challenges associated with the use of unlicensed 'special' medicines, such as short expiry dates and increased costs and described how this impacted their ability to automatically supply medicines to patients in a community pharmacy.

*"I think because of the cost of the special we wouldn't have kept it in [the pharmacy] just in case, especially with it only having a 28-day expiry... so if we ordered it in advance and then [the patient] didn't come in for another week or so, then it's cutting into the expiry of the actual item" [INT 1.3].*

The cost and short expiry dates seen with some unlicensed 'special' medicines limited the possibilities for storage within the pharmacy. Participants reported how the limited expiry dates also affected the process of ordering repeat prescriptions for unlicensed 'special'

medicines. Participants described not ordering unlicensed 'special' medicines automatically as in some cases the medicine may run out before expected in which case the patient would need another supply sooner than anticipated, or if the medicine was ordered too early this would cut into the already short expiry date before the patient would begin using it.

*"We don't tend to order [unlicensed 'special' medicines] automatically because it varies, (pause) you know in theory it should run out at this time, but it seems with [short] expiry dates and with liquids especially, especially if it's being administered and the nurses are pouring it, it doesn't always last as long as you'd expect it to" [INT 1.2].*

Participants agreed that due to these issues, patients would need to inform the pharmacy prior to when the unlicensed 'special' medicine would be needed in order to allow enough time to ensure the pharmacy could obtain it. The amount of notice given or needed, varied among patients ranging from a few days to around a week.

*"[The patient] rang Tuesday and they'll probably run out over the weekend, so they'll need it the beginning of next week, well that's a realistic timeline, it gives us two days to order the prescription, day for the special, got the weekend and a day for emergencies" [INT 1.2].*

The need for patient-led management of ordering was described as an effective method in maintaining a continuous supply. Participants explained to patients when they initially presented a prescription for an unlicensed 'special' medicine to the community pharmacy the need for this responsibility and would encourage patients to adopt this method.

*"We try very hard to train our patients [when ordering unlicensed 'special' medicines]" [INT 1.2].*

Participants detailed how if this responsibility was not handled correctly, and the GP or the pharmacy were not informed with enough notice, the patient themselves could be the cause of delays or disruption to supply. Participants described how if the prescription was not ordered in advance from the GP, this would disrupt the ability of the community pharmacy staff to order the unlicensed medicine in and delay access for the patient.

*"We have this one patient who, has a particular item that only has a 28-day expiry and then [the patient] left it a bit late to order the prescription, so then obviously we couldn't order the special, so yeah I guess in that situation, then the patient would have suffered, had we not been able to get it to them in time" [INT 1.3].*

If the patient does not take on the responsibilities, this could impact the success of accessing the medicine when needed. Patient initiated ordering was reported to help manage the timelines involved when accessing prescriptions and supplies of unlicensed 'special' medicines and aided participants in ensuring the continuity of treatment.

#### **4.5.2.2 Theme 2 - Influences on the confidence felt by pharmacy staff when accessing and supplying unlicensed 'special' medicines**

Multiple factors were highlighted that affected the confidence felt by participants when acquiring and supplying unlicensed 'special' medicines. This included the complexity of these medicines and the amount of relevant clinical information received across care settings. Participants considered how professional trust towards prescribers and suppliers and their own personal level of experience helped to reduce concerns around the use of unlicensed 'special' medicines and increase the confidence felt when acquiring and supplying these medicines to patients.

##### **4.5.2.2.1 Ambiguity about classification and processing of unlicensed 'special' medicines**

While all participants were aware that unlicensed 'special' medicines were not licensed for use, the definitions given varied with some describing unlicensed 'special' medicines and others describing 'off-label' medicines, revealing different interpretations of the guidelines and varying perceptions among participants.

*"[An unlicensed 'special' medicine is] something that's being used away from the product license, meds that are licensed for one use and then used for different conditions" [INT 1.3].*

Participants acknowledged the complexity of unlicensed 'special' medicines and reported that they adopt a more cautious approach when dealing with these medicines compared to when acquiring and supplying licensed medicines.

*"There's lot of particular issues which we would look at in a general prescription, but we tend to be much more cautious [with prescriptions for unlicensed 'special' medicines]" [INT 1.1].*

As a result of the varying levels of safety and efficacy evidence available for unlicensed 'special' medicines, participants reported less confidence when receiving prescriptions for 'specials' that were unfamiliar to them or that were not commonly used, and again reported a more cautious approach.

*“If we’ve only got one patient on [an unlicensed ‘special’ medicine] and I can’t find anything where another patient has been on a dose similar or, or [sic] used in that indication then perhaps I might be a little bit more cautious” [INT 1.4].*

Depending on whether the requested medicine was commonly used as an unlicensed formulation or with an unlicensed dose or indication, or the prescribing pattern was more experimental, participants felt different levels of confidence when dealing with the request, as the level of available information about the medicine varied. In these cases, participants highlighted the need to spend time researching the literature in order to feel confident enough to continue with the prescription.

*“I do a little bit of research and possibly on the internet to see if [the unlicensed ‘special’ medicine prescribed has] been used commonly or whether it’s something I’ve never seen before, and then once I do those bits of information gathering then I’d make a decision as to whether I was happy to sign it” [INT 1.4].*

When unusual or experimental unlicensed ‘special’ medicines were prescribed, participants reported seeking information about the medicine and highlighted the types of information they would want to access to increase their confidence when supplying these medicines. This included using the BNF, BNFc and seeking information about the previous uses and clinical efficacy of the medicine for the condition being treated.

*“I’m learning on some of the [unlicensed] drugs, so we’ve had two that I’ve had to do some background research for my own satisfaction just to find out the clinical efficacy” [INT 1.1].*

The complexity of unlicensed ‘special’ medicines, including their uses for a wide range of indications, with a wide range of dosing regimes, and with different formulations, as well as the perceived limited evidence available for uncommon unlicensed medicines, was seen to impact pharmacy staffs’ perceptions of confidence and approach to processing prescriptions. This resulted in a more cautious approach when processing prescriptions and seeking further information about the uses of the unlicensed ‘special’ medicine to help justify its use.

#### **4.5.2.2.2 Information needs for safe transfer of care across settings**

A lack of access to patient-specific clinical information to accompany prescriptions for unlicensed ‘special’ medicines across care settings was reported by participants. All participants who had experienced receiving a new prescription for an unlicensed ‘special’ medicine agreed that they would need to seek further information from the prescriber before feeling confident enough to process and supply the medicine.



*“If the dose is unlicensed, then the first thing I would do is speak to the prescriber [GP], Just to get a bit of context, and a bit of background, obviously they’ve got access to a lot more notes than I have” [INT 1.4].*

One participant described how if further information was provided alongside prescriptions for unlicensed ‘special’ medicines, this could help to reduce the workload within the pharmacy, as staff would not need to contact others in order to gain an understanding of why the medicine was prescribed and the clinical context for the patient.

*“It took a call to the surgery, a call to the hospital and a call to the patient, whereas if I’d had that information with the prescription, ‘this is an unlicensed medicine, the dose has been checked by a kidney specialist, the patient has been on it for years and years, well, and it goes on, that would probably have saved me a bit of time” [INT 1.4].*

However, not all participants were challenged by the lack of information described above when a prescription for an unlicensed ‘special’ medicine was received from secondary care, on the contrary, some participants described positive experiences and explained that clinical information was provided from the hospital. In particular, this included information about the justification for the use of an unlicensed ‘special’ medicine.

*“What the hospitals have been doing recently is actually been giving me a back sheet, with some indications of why this is being prescribed, that’s really valuable” [INT 1.1].*

Receiving clinical information across settings increased the participant’s confidence when acquiring and supplying unlicensed ‘special’ medicines and reduced the workload within the pharmacy as the participant did not have to seek further information to justify or confirm the prescription. However, this was not the only information participants had to access in order to make informed decisions. One participant described how a lack of clinical information received with the medicine from the suppliers led to delays in supply while awaiting the paperwork associated with the unlicensed ‘special’ medicine supplied.

*“I’ve used other [suppliers] in the past and the paperwork turns up sort of separately, and it’s just \*shakes head\*....well you’re holding the prescription back, you’re waiting and oh you’re chasing it up, I don’t like it, I much prefer to have everything, drug comes in, paperwork’s there, everything’s neat and tidy (laughs)” [INT 1.2].*

This participant did not feel confident to supply the unlicensed ‘special’ medicine until they had received the product information and certification from the supplier. Other participants

described situations where limited information was received from prescribers in primary and secondary care and from suppliers. This included information about the justification of the prescription, the medical context of the patient, or the product information about the actual medicines received, all of which led to decreased confidence and an increased workload for participants, while they sourced the information.

#### **4.5.2.2.3 Accepting expertise of other healthcare professionals**

When acquiring and supplying unlicensed 'special' medicines, participants reported a sense of professional trust towards healthcare professionals across the supply chain such as prescribers and suppliers, and described how this widely accepted hierarchy of trust inevitably contributed towards reassuring them of the suitability of the medicine, even with their perceived lack of confidence.

*"[Unlicensed 'special' medicines], well, they're prescribed from upon recommendation from the consultant, so I guess we all just have trust in the consultant that they've recommended something that's suitable" [INT 1.3].*

When dealing with unfamiliar or unusual unlicensed 'special' medicines, participants described how they would seek clarification from the primary care prescriber, and how both parties (primary care prescriber and participant) would ultimately need to refer to the judgement of the original prescriber, whom they perceived held specialist knowledge. This acceptance of professional trust and the perceived knowledge and experience of secondary care prescribers helped to increase participants' feelings of confidence in the need and suitability of the unlicensed 'special' medicine prescribed.

*"If the prescriber [GP] tells me that the consultant or the specialist in a unit somewhere has prescribed [the unlicensed 'special' medicine], then that person has expertise in prescribing that kind of drug, in which case, although I might not feel comfortable with it, I wouldn't go against what somebody says if they've got twenty years' experience in a field" [INT 1.4].*

Participants discussed how trust in the perceived knowledge and level of expertise of the original prescriber directly impacted the confidence felt when dispensing unlicensed 'special' medicines, even when they were not actually comfortable with the prescription themselves suggesting a need for participants to rely on this trust in order to successfully continue supply. The sense of professional trust felt towards prescribers was also reported to help ease any concerns felt by participants about the safety of unlicensed 'special' medicines for children, as it was understood that for the medicine to have been prescribed, the prescriber must have assessed the patient and potential risks to determine a suitable treatment.

*“Well, I guess, it’s more sort of a dangerous feel to sort of mess about with children and elderly patients, so, yeah I wouldn’t really, it’s probably not the safest thing to experiment with unlicensed meds in children.... But then I guess then (pause), the prescribers then (pause) sort of assessing the risk benefit, depending on the child’s size, might be a big child, small child, so yeah, I guess” [INT 1.3].*

The professional trust felt towards the prescriber was seen to halt concerns being raised and served as assurance to participants. Another participant gave an example of how the professional trust felt towards primary care prescribers reviewing treatments based on national prescribing guidance reinforced their own preconceptions about the need to continue the supply of a specific unlicensed ‘special’ medicine.

*“We’ve had it with the Armour Thyroid [unlicensed medicine], where some surgeries have started to refuse doing that, you know...but they’re basing it on NICE guidance and, health authority guidance, so you know I’m not going to argue with that because, to be honest, I, don’t, think, we should be paying hundreds of pounds for it either...I haven’t had an issue with, them refusing to do a special when it’s been, needed, so (pause) if that makes sense, (pause) although then someone on Armour Thyroid would argue that it’s needed but there we are” [INT 1.2].*

Participants highlighted how professional trust that the suppliers followed protocols and that they complied with MHRA guidance for manufacturing and supplying unlicensed medicines helped to increase the confidence felt around the safety of the unlicensed ‘special’ medicines supplied.

*“Yeah, we don’t use any sort of dodgy suppliers or anything, so as long as they’re regulated by the MHRA then we’re quite happy that if they’ve got a licence from them to produce, then they should be producing to a sort of standard” [INT 1.3].*

Awareness that there are manufacturing standards and regulations around the use of unlicensed ‘special’ medicines helped participants to feel more confident about the quality of the medicines supplied. The certification received from suppliers was also seen as a factor that helped to increase the trust felt towards suppliers and the perception that the medicines would be safe.

*“I work on the fact that if [an unlicensed ‘special’ medicine has] got [certifications], then it’s manufactured as per guidance, and you know (pause) the drug I can look that part up, to know you know that it is being used for the right thing and they’ve got a certificate of conformity and that, then it’s been manufactured properly” [INT 1.2].*

The professional trust and perceived responsibility of manufacturers to maintain a standard, helped to increase participants' confidence and was also reported to combat any concerns participants may have had about the safety of the unlicensed 'special' medicines.

*"Hmm (pause) safety of [unlicensed 'special' medicines could be targeted]? (pause) I don't know, make sure, I'm sure it's pretty safe isn't it, and they make it all safely and with the regular ones have made it a thousand times (pause) yeah" [INT 1.6].*

The perceived trust and responsibility of others reduced the concern being raised by the participant. The responsibility of others involved in the supply chain helped participants to feel more confident about their role in supplying unlicensed 'special' medicines to patients, as other professionals would have been involved in determining the suitability of the prescription for the patient, and the safety of the product through testing. However, it was clear that much of the trust described above was a result of a need on behalf of the participants, as there would be no way for a community pharmacy staff member to be able to have the clinical expertise of a secondary care specialist prescriber, in order to judge the clinical suitability of unlicensed medicines, or to have the knowledge and expertise on how unlicensed medicines are manufactured like suppliers would. One participant described how, as there are multiple stages involved throughout the supply chain, relying on the professional trust is a more of a necessity than a requirement in order to keep the supply chain moving.

*"There needs to be an element of professionalism to know, that what comes in is legitimate and has gone through the correct testing...but also, there's got to be an element of, you can't do everybody's job previously for them, if [the unlicensed 'special' medicine is] presented with the correct documentation then I'm happy with that" [INT 1.4].*

The participant described a need for this professional trust as their role in supplying unlicensed 'special' medicines is just one step in the supply chain. Overall, the professional trust felt towards the original prescribers, manufacturers and suppliers were all reported to increase participants' confidence when accessing and supplying unlicensed 'special' medicines.

#### **4.5.2.2.4 Association of confidence with experience within the role**

Participants described how their own personal views and experiences as a community pharmacy staff member affected their confidence when acquiring and supplying unlicensed 'special' medicines. Participants viewed their role of supplying unlicensed 'special' medicines as important and necessary to meet the needs of the patient.

*“I’ve got quite a lot of responsibility, yeah because if the patients need their medicines and if it is a special then obviously, we have to obtain that special then to fulfil the patients’ needs” [INT 1.5].*

All participants viewed their role seriously and understood that the clinical need of the patient may justify the use of an unlicensed ‘special’ medicine. However, participants with more experience acquiring and supplying unlicensed ‘special’ medicines reported a more relaxed view of their role.

*“Well I think [the role of accessing and supplying unlicensed ‘special’ medicines is], part of my job, it’s y’know [sic] we should be, if a patient has been prescribed an item, (pause) within reasonable grounds we should be able to supply it” [INT 1.1].*

One participant reflected on their own experiences and described how their concerns around safety in relation to supplying unlicensed ‘special’ medicines to patients when first taking on the role of a community pharmacist had decreased, and their confidence had increased over time.

*“I think when I first qualified, even a one daily [unlicensed ‘special’ medicine] kept me up in the night cause it’s the first time I ever really signed things like that away, but I think in the start when doses were different to what you’d see with licensed items it was a bit, hard to sign it, just purely because no experience, and the worry that something might possibly happen to the patient and that my name is against it... but as time has gone on, with experience, I know the right calls to make” [INT 1.4].*

The longer the participant was exposed to accessing and supplying unlicensed ‘special’ medicines, the more their confidence and perceived abilities to do so in the future increased. Participants described how their knowledge and previous experience seeking information about unlicensed ‘special’ medicines had helped them to feel more confident when processing prescriptions.

*“There’s a lot of information out there [for unlicensed ‘special’ medicines] it’s not always as easy to find as it is for, your general Joe Bloggs, but it’s available to find you just have to look a bit harder sometimes” [INT 1.2].*

Although participants reported difficulty in sourcing information about unlicensed ‘special’ medicines, the participants knowledge and experience finding information about medicines in the past helped them to feel more capable of accessing this information in the future. Participants described how positive experiences with suppliers when accessing and supplying unlicensed ‘special’ medicines also helped to increase their confidence.

*“I’m quite confident about [the suppliers], yeah, (pause) and if I’ve ever got any questions or queries, they’re always very helpful” [INT 1.2].*

Experiences of a consistent, reliable service helped to increase the participants’ confidence in the suppliers used. Participants also described positive experiences where the supplier was involved in reducing delays by speeding up the delivery time when a prescription had been received late. This experience helped to establish a good working relationship between the pharmacist and the suppliers used.

*“I had one instance and it was just prior to uh the Christmas vacation last year, and a prescription [for an unlicensed ‘special’ medicine] was very late in coming through, and I put it through and I asked [the suppliers] if it could be done as ‘super urgent’ for me, and literally they were here at nine thirty in the morning... so you know, we don’t have to do that very often, but they responded, they realised, you know that we needed that” [INT 1.1].*

Just as positive experiences helped to increase the confidence felt by participants, a lack of negative experiences was also seen to help participants feel more confident when accessing and supplying unlicensed ‘special’ medicines. Some participants had not experienced any cases where the patients’ treatment with an unlicensed ‘special’ medicine was disrupted due to any issues or delays.

*“I haven’t had any instances where patients have been without [unlicensed ‘special’] medicines, because of a delay, or because there’s something wrong with it or because there’s something I needed to check, never had that yet, so if I had something like that, that would be an issue I would want to raise, but at this time every patient I’ve had has had it in the right amount of time, and has been absolutely fine” [INT 1.4].*

Each participants’ individual views and experiences impacted their perceived confidence when acquiring and supplying unlicensed ‘special’ medicines.

Overall, there are multiple factors that affected the confidence felt by community pharmacy staff when processing prescriptions for unlicensed ‘special’ medicines. Participants highlight how a lack of information and the ambiguity around the classification of unlicensed ‘special’ medicines led to a reduction in the confidence they felt, but experience in the role along with professional trust and good established working relationships with suppliers, helped to increase their confidence and reduce their concerns.

### 4.5.2.3 Theme 3 - Continuity of supply

Participants described several factors that were seen to impact the continuity of supply for unlicensed 'special' medicines. Keeping additional records about the 'specials' supplied and the use of an online ordering system was reported to help maintain continuity of supply. However, tensions between care settings and issues with the accessibility of unlicensed 'special' medicines were still experienced, occasionally resulting in supply delays and even treatment disruption.

#### 4.5.2.3.1 Additional record keeping

Additional record keeping, both in the patient medication record but also on a separate file specifically recording the use of unlicensed 'special' medicines, was described as being required by participants before authorising the ordering of a 'special' medicine. As there are no official guidelines on standardisation of format or information included in these additional records, participants were relying on the company's SOPs for recording.

*"All details then are put on the patients PMR the online record, but we do keep paper records of of [sic] the compliance and it's in a special file, that's a requirement for our SOP, so the SOP would like PMR updated and the specials file updated as well" [INT 1.1]*

Participants described how recording the supply of unlicensed 'special' medicines differed when compared to licensed medicines. The additional information recorded increased transparency within the pharmacy and was helpful for future re-ordering, as the pharmacist would make notes on where the medicines were originally obtained from and specific details of the medicines ordered.

*"If it's something new, then I'm likely to, do it myself first, find out where we get [the unlicensed medicine] from, then we put a note on the patients record so that in future, somebody else could continue the ordering" [INT 1.4].*

Participants explained how the additional records kept were also useful when dealing with external queries about the cost of the medicines for reimbursement, as staff members were easily able to confirm details with the pricing bureau by looking at the records.

*"The prescriptions are sent to our pricing bureau in Cardiff, if there's any issues then they will phone me, and occasionally they will phone me and they say 'can we just confirm please the price of this particular drug'... there was one time when we were supplying a very, very expensive drug, and so they would phone me and I would give them all the details of the PMR and a bit of background" [INT 1.1].*

Conversations with prescribers and patients were also recorded within the pharmacy, this typically involved confirmations of the prescription details with prescribers and the patients acknowledging the supply of, and details around the use of their unlicensed 'special' medicine.

*"I confirm with the prescriber and understand the patient knows exactly, what the dose is, the fact that the dose is not licensed, and I usually document that on their records then to say they've acknowledged it" [INT 1.4].*

Overall, the additional records kept by participants were not only useful in terms of keeping product specific details about the use of unlicensed 'special' medicines, but were also seen as a method of noting conversations had with prescribers and patients. The recording of information about the suppliers used and specifics of the medicine ordered was described to aide others within the pharmacy and maintain continuity when ordering further supplies in the future.

#### **4.5.2.3.2 Tensions within and between care settings**

When trying to ensure the continuity of unlicensed 'special' medicines between care settings, participants reported the importance of healthcare professional awareness and consistent levels of acceptability. Participants described how inaccuracies on the prescriptions received or with the product selected on the GP prescribing software could lead to friction between pharmacy and GP staff, with potential for increased costs to the NHS.

*"Often [the GP surgery] just forget to put the quantity on [the prescription], and sometimes we have to return the prescription for them to have the quantity added on, they're the only sort of problems really" [INT 1.3].*

Inaccuracies on prescriptions received for unlicensed 'special' medicines such as having the wrong quantity prescribed was an error that the community pharmacy that staff needed to correct, increasing the workload within the pharmacy and delaying the supply of the medicine. However, a lack of awareness was also reported to lead to more serious prescription errors.

*"I mean we had some last year, with the flu vaccination and two of the [GP] surgeries I think, or it might even have been three of the surgeries, picked the specials liquid for the anti-viral by mistake, instead of the licensed one" [INT 1.2].*

One participant had experienced multiple occasions where unlicensed 'special' medicines had been mistakenly prescribed by GPs when they had not realised they had selected an unlicensed product. The participant explained how mistakes like this disrupted the workflow



within the pharmacy, and delayed the pharmacists ability to acquire and supply the medicine needed, while the prescription was corrected.

*“We had a word with the surgery, got a new prescription and did that one...that probably causes more time than actually having a special prescription” [INT 1.2].*

The GP lack of awareness described when prescribing unlicensed ‘special’ medicines was seen to increase the workload within the pharmacy and delay community pharmacy staff when trying to supply the medicine. One participant reflected on how even when healthcare professionals were aware that an unlicensed medicine was required, they perceived a difference in outlook when it came to the acceptability of unlicensed ‘special’ medicines across primary and secondary care. The participant perceived secondary care prescribers to have increased perceptions of acceptability when compared to GPs.

*“In hospitals they’ve got consultants, and consultants have a far wider brief, as regards to prescribing, so they can step outside of certain limitations and when a patient then is transferred to the community, what was ok in a hospital is not necessarily ok with the community GP” [INT 1.1].*

The participant had previous work experience in a hospital setting and explained their perception as to why there were differing levels of acceptability between care settings when it comes to supplying unlicensed ‘special’ medicines. This was perceived to be due to differences in practice, with secondary care prescribers using a wider range of unlicensed ‘special’ medicines compared to GPs and this was believed to directly relate to acceptability. Tensions were also mentioned in the interface of primary and secondary care, mainly linked to the differences in acceptability among healthcare professionals across care settings that were seen to lead to delays.

*“The issue that I still find a little irksome, is when we have an ADHD child, whose been prescribed a drug by their hospital paediatrician and their GP has refused to do the follow on... it’s known as shared care, and there’s generally an agreement between the two, and it doesn’t happen as often as it used to... but it still happens” [INT 1.1].*

Participants outlined how the variation in perceived acceptability across primary and secondary care could disrupt the continuity of supply when GPs refuse to continue prescriptions for unlicensed ‘special’ medicine that have been previously initiated. However, a variation in perceived acceptability was not just reported across care settings, but also among individual healthcare professionals in the same care setting. The participant described how individual GPs had varying levels of acceptability and when the responsibility

to continue a prescription for an unlicensed 'special' medicine was passed from one GP to another, this could lead to GP refusal even if the medicine had been supplied regularly by the surgery before.

*"We've had a few where historically where the GP has prescribed [an unlicensed 'special' medicine] and then where the GP that had prescribed it has retired, and then the new GP is going 'why are we doing this?, I'm not doing this'" [INT 1.2].*

The individual perceptions of healthcare professionals on the acceptability of unlicensed 'special' medicines directly impacted the continuity of supply across care settings. Participants described how having multiple healthcare professionals involved in the supply chain and across different care settings meant there are numerous opportunities where continuity could be interrupted as a result of differing perceptions of acceptability, for example, when locum GPs are needed to cover for regular GPs.

*"I have one patient who, (pause) the surgery will often have a locum in place, and I understand if the locum doesn't feel comfortable about signing a repeat prescription for this [unlicensed] drug, but it's landing that patient's care... you know suddenly their, perhaps their regular doctor might not be in until the Friday which means, it's a controlled drug I have to get that prescription" [INT 1.1].*

In the situation described above, the patient periodically had to wait longer than desired to access their medicine due to the locum GPs perceived lack of acceptability of the unlicensed 'special' medicine prescribed. This caused ongoing experiences of delay for the patient and limited the ability of the pharmacy to ensure the continuity of supply. Participants explained how the tensions described above can directly impact the continuity of supply, with prescription errors and individual perceptions of acceptability causing delays obtaining the prescription when needed.

#### **4.5.2.3.3 Challenges with accessibility**

When the community pharmacy had received a repeat prescription for an unlicensed 'special' medicine, they were responsible for maintaining the supply. Participants described how this responsibility was shared within the pharmacy.

*"I tend to [order] the specials, we've got a few patients on regular specials and then my technician could handle that" [INT 1.1].*

Technicians and dispensers were reported to order in repeat prescriptions for unlicensed 'special' medicines however, the pharmacist was primarily responsible for the clinical checks when processing a new prescription and sourcing the first supply. Accessing the first supply

of an unlicensed 'special' medicine was described as more time consuming compared to ordering repeats.

*"[Staff in the pharmacy are] familiar with the process [of processing repeat prescriptions for unlicensed 'special medicines] so it's fairly streamlined, and I think that makes a difference, I think it's harder if it's not something you do on a regular basis.... it takes us longer if we have a new one because we're checking, you know we're checking a lot more you know where we can get it from, lead times" [INT 1.2].*

Once the unlicensed 'special' medicine had been ordered into the pharmacy the process of accessing repeat prescriptions was described as less time consuming as staff would not need to identify a supplier and would know how long the lead times would be. However, participants outlined some challenges faced when trying to maintain a continued supply of unlicensed 'special' medicines, even including delays caused by bad weather.

*"We've had in the past where [the unlicensed 'special' medicine has] been lost, you know in transaction, that's happened when it's snowing you know, when it's like really bad weather and they can't get to us as fast" [INT 1.6].*

These sort of issues, although not reported to be frequently experienced, still had an impact on the continuity of supply. A sudden increase in the timeline involved when obtaining an unlicensed 'special' medicine from the supplier was described by one participant. To ensure the continuity of supply the pharmacy staff had to adapt and order the medicine further in advance.

*"There has in the last three months been a 7-10 working day wait [for an unlicensed 'special' medicine]....that has been difficult in the past because the patient has almost run out if it, but of late they've been sending it the next day, so it must've just been an ingredient issue or a manufacturing issue that caused the longer time" [INT 1.4].*

When unlicensed 'special' medicines have been on repeat prescriptions and are regularly ordered into the pharmacy from one supplier, issues with accessibility like the example above, can still take place at any point and disrupt the continuity of supply. One participant described how even when the unlicensed 'special' medicines are accessible from suppliers, there may be a lack of consistency in the actual medicine received.

*"What will sometimes happen though particularly with one of the drugs the melatonin drug for the youngsters, the flavours will alter because there's a big push for sugar free.... and of course these children notice" [INT 1.1].*

Although not a big change, the difference in consistency of taste or flavour can directly impact the patient and their acceptability of the medicine, specifically in children. Other issues with the consistency of a specific medicine or form were also reported by pharmacy staff, such as availability of gels or creams.

*“There’s been, like GTN cream or gel if one is available and the other one isn’t, but then, we would just supply what we can get really” [INT 1.5].*

A lack of consistency in the specific forms available impacted the ability of pharmacy staff to maintain continuity of the supply of the specific unlicensed ‘special’ medicine prescribed. Participants reported having to adapt their process within the pharmacy by using multiple suppliers in order to ensure the supply could be maintained.

*“[The suppliers] didn’t have a solution they only had a suspension so, we couldn’t use them in the end for that for that item... we had to go to someone else to order it... and then that wasn’t as straight forward” [INT 1.6].*

The lack of availability of specific unlicensed ‘special’ medicines in specific forms caused an increased workload for pharmacy staff, as they had to identify alternative suppliers. One participant reported how a lack of accessibility had a direct impact on patient care when the medicine could not be obtained.

*“Three years ago... we were unable to get the medication in and the patient had a lapse of three days... in this case, no other pharmacy could supply... the hospital couldn’t supply after... and so the patient was without medication for three days, they were monitored and they didn’t suffer adversely, but it’s not a situation that I would ever like to be in” [INT 1.1].*

In this case, the lack of accessibility of the unlicensed ‘special’ medicine prescribed was seen to disrupt treatment and the continuity of supply across multiple settings, as the prescribing hospital could not access the medicine either. Accessibility issues such as this, make it difficult for the pharmacy staff to maintain the supply and provide continuity for patients.

#### **4.5.2.3.4 Perceived advantages of online ordering**

Participants described how technology was used to reduce the time and workload involved when ordering unlicensed ‘special’ medicines, as all the participants were from one small chain of community pharmacies, most were using the same supplier with an online ordering system.

*“We can order [unlicensed ‘special’ medicines] online....they will respond to me within two hours if there is an issue with supply, if there isn’t an issue with supply I just get a quick email to say it’s on its way, it’ll be with you before twelve tomorrow and, it’s superb (laughs)” [INT 1.1].*

Participants described the ease of the online ordering system and perceived this use of technology to be valuable when accessing and supplying unlicensed ‘special’ medicines. The participants described an increase in the speed of communication with the supplier by being able to receive email updates and confirmations rather than having to phone the supplier.

*“I prefer it online, cause it just saves time, sometimes other special companies can take ages to answer the phone, and when you’re in a busy pharmacy you just want to get online, send your order and then let it be, let it process, while you carry on with your job” [INT 1.4].*

The online ordering system was seen to reduce the workload within the pharmacy by reducing the amount of communication and follow up needed when ordering unlicensed ‘special’ medicines. Another process that facilitated ordering and led to minimal delays when adopted by the suppliers was the “named patient” ordering, where an initial order was linked with a specific product and an individual patient, and any subsequent orders used this same information.

*“The thing about a special, the patient needs it, fairly quickly and what we’ve found with this particular company is they understand that, we can order online, they respond to the order, the details, all the details go on, including the name of the patient ok, we do it as a named patient, it improves tracking... rather than just give them a number, we do it under a named patient issue.” [INT 1.1].*

The online ordering system and the “named patient” ordering process was described to improve tracking of the product and reduce the workload in the pharmacy. One pharmacy had not yet switched over to using the online supplier at the time of the interview. A different process was described when ordering unlicensed ‘special’ medicines and not using the online system, which involved the need for increased communication with the manufacturers and a longer process in confirming details of the medicine required.

*“We’ve got sort of fact sheets that we use for our regular specials, so it’s like a pro forma that we use, we’ll fax that off to the manufacturer, they’ll give us a ring back to confirm it, they’ll then send us an email, with everything in confirming it, letting us know what their expiry date is, pack sizes and if there’s any issues, we’ll then reply to*

*that email confirming it and then it'll come in, they'll usually tell us when we'll be getting it as well, that usually comes in then the next day" [INT 1.2].*

The participant was aware of the upcoming change of suppliers and anticipated how the online ordering system would reduce the workload within the pharmacy when ordering unlicensed 'special' medicines and speed up the entire process, by reducing the amount of communication needed with suppliers and improving the ease of tracking the delivery.

*"I think the new supplier we're going to switch to, has got an online ordering system, and I think that'll probably help streamline [the process of accessing unlicensed 'special' medicines] as opposed to phoning all the time, so that would be quicker, and you can track it online then, so I suppose that's an improvement that we've already got coming through" [INT 1.2].*

Overall, participants described positive and negative factors that impacted the continuity of supply. The additional records kept were helpful in maintaining the supply of the medicines and the online ordering system helped to reduce the workload associated with ordering specials. However, the continuity was reported to be disrupted by the tensions between care settings and the issues experienced around accessibility.

## **4.6 Discussion**

The aim of study 1 was to explore the views and experiences of community pharmacy staff when accessing and supplying unlicensed 'special' medicines. To the researcher's knowledge the results of this study offer the first insight into the views and experiences of community pharmacy staff specifically in Wales. The results highlight the important role that the patients themselves play in maintaining communication to ensure medicine supplies are consistently accessed and the need for patient awareness to support this process. Positive and negative factors were identified that impacted the confidence felt by participants when obtaining and supplying unlicensed 'special' medicines, such as the benefits of an online ordering system or a lack of clinical information received with prescriptions across care settings. The participants also described some of the challenges faced and the adaptations to the workflow that were used in order to ensure the continuity of supply and successful treatment. Despite the efforts made by pharmacy staff, delays and disruption were occasionally experienced. The findings provide a detailed insight into the views and experiences of community pharmacy staff.

Participants outlined the additional responsibilities that patients receiving unlicensed 'special' medicines were expected to take compared to patients receiving licensed medicines, mainly

informing the pharmacy prior to when the medicine would be needed to allow enough lead time for the pharmacy team to acquire the medicine. This was required due to the varying timelines involved in acquiring unlicensed 'special medicines and the short expiry dates limiting possibilities for storage within the pharmacy or the option to automatically re-order products. These issues have been reported previously in the literature (Venables *et al.*, 2015; Husain, Davies and Tomlin 2017; Rawlence *et al.*, 2018) supporting the findings of this study. Evidence has also been reported previously supporting the need for patients to take part in additional actions in order to counteract these issues and maintain continuity such as increased contact with pharmacy staff and requesting assistance from other healthcare professionals (Husain, Davies and Tomlin 2017). This suggests that patients receiving unlicensed 'special' medicines are routinely needed to be involved in the process of acquiring them in the community.

For patients to successfully take on board the additional responsibilities required they must be aware their medicine is unlicensed and must be informed about the implications of receiving an unlicensed 'special' medicine, such as the short expiry dates and the need to inform the pharmacy in advance of when further supplies were needed. Participants described varying levels of awareness in patients receiving unlicensed 'special' medicines and outlined how when patients were not aware of the associated increase in lead times, this could lead to delays in acquiring the medicine and therefore could disrupt the continuity of supply. This is concerning as the literature has shown that in the UK the general public lack awareness around the use of unlicensed 'special' medicines (Mukkatash *et al.*, 2008).

Participants reported having discussions with patients about the licensing status of their medicines and described the balance that was needed between informing patients about their unlicensed 'special' medicines and the practical implications of receiving these from a community pharmacy, without causing undue concern. Participants provided examples of the concerns patients receiving unlicensed 'special' medicines had shared with them, such as questioning the need for the medicine itself. The increase in concerns reported by patients once fully informed about the use of unlicensed 'special' medicines has been reported previously in the literature (Mukattash *et al.*, 2019; Aston, Wilson and Terry 2019) and could have potential implications on adherence behaviours (Clifford, Barber and Horne 2008; Horne *et al.*, 2013). To the researcher's knowledge, there are no previous studies exploring adherence behaviours specifically in relation to receiving unlicensed 'special' medicines. Further research would need to be conducted to explore the perceptions of need, in order to better understand adherence behaviours in patients' receiving unlicensed 'special' medicines.

To improve the awareness of patients receiving unlicensed 'special' medicines without causing undue concerns there are several methods that could be adopted, such as educational interventions and patient information leaflets. Educational interventions, such as short videos co-designed with patients and available on free platforms such as YouTube, could be used to inform patients about the implications of receiving unlicensed 'special' medicines. Successful educational interventions have previously been used to improve patient awareness for a range of conditions such as chronic kidney disease (Lopez-Vargas *et al.*, 2016), hepatitis B and C (Shah and Abu-Amara 2013), and multimedia educational interventions have been found to improve knowledge around prescribed and over-the-counter medicines (Ciciriello *et al.*, 2013).

Overall, to reduce the likelihood of patients receiving unlicensed 'special' medicines and being unaware of the unlicensed status, and the resulting implications to practice, a common resource is needed that could be supplied to patients across care settings. Across the UK, information leaflets have been created locally within the NHS but have not been standardised for wider use: examples of this have been created by Gloucester hospitals (NHS 2018), Oxford University Hospitals (NHS 2016) and York teaching hospital (NHS 2010). The leaflets created not only include information covering what unlicensed medicines are, but also some practical advice about the timelines involved in obtaining unlicensed medicines and information related to potential concerns that patients may have. By providing an agreed information resource for patients, it should help to achieve consistent levels of awareness and understanding in patients receiving unlicensed 'special' medicines while addressing any concerns they may have.

The results of this study highlighted how it was not just patients that had a lack of awareness around unlicensed 'special' medicines, but also the community staff participants themselves. The range of definitions provided by participants for what an unlicensed 'special' medicine is, reflect the inconsistent terminology provided in the existing guidance available to them and within the literature. This lack of consistent information has been suggested to be another contributing factor to propagation of the risks associated with the use of unlicensed 'special' medicines (Donovan *et al.*, 2016) and this study further supports the highlighted need for clear and consistent information to be created for healthcare professionals across care settings.

Participants in this study outlined factors that were seen to impact their perceived confidence in their ability to acquire and safely supply unlicensed 'special' medicines. Factors that decreased their confidence mainly consisted of a lack of available information about specific preparations and the lack of access to patient-specific clinical information to accompany



prescriptions across settings. As there are a myriad of medicines that are considered unlicensed 'special' medicines, the level of evidence available can vary dramatically meaning the individual preparation itself can impact on the confidence felt by community pharmacy staff. Participants described seeking further information about unlicensed 'special' medicines that were unfamiliar to them as some 'special' preparations are more commonly seen than others. In addition to this lack of information available for the use of some unlicensed 'special' medicines, participants also described a variation in the amount of information received with prescriptions about the clinical need and justification for the medicines' use.

It is widely recognised that transfer of care across settings is an area where medication errors often occur (WHO 2019a). To combat this, initiatives have been introduced to improve communication during transfer of care and minimise associated risks, however community pharmacists are not typically provided with information about discharge medicines (Wilcock and Bearman 2019). Participants described the lack of accompanying clinical information received with prescriptions for unlicensed 'special' medicines as a significant factor that reduced their confidence to acquire and supply the medicines.

Participants outlined how they would often seek further information either about the clinical efficacy of the medicine or the clinical need by contacting the original prescriber either in primary or secondary care before they felt comfortable to supply the medicine. One participant had described receiving some information about the clinical need of the medicine from hospitals who initiated its use, which resulted in an increase in confidence and reduced the need for the participant to seek further information.

Participants described further adaptations they had made to ensure the successful supply of unlicensed 'special' medicines such as keeping additional records compared to licensed medicines not only as a legal requirement (HMR 2012) but also to increase transparency within the pharmacy, recording conversations had with patients and details of previous orders so that others could easily re-order medicines. Additional records were also kept to document participants' professional judgements as discussed in guidance by the professional (Royal Pharmaceutical Society 2015) and regulatory (General Pharmaceutical Council 2018a) bodies for pharmacists in the UK.

In Wales, the Discharge Medicines Review Service was introduced in 2011, (Hodson *et al.*, 2014), and has been associated with reduced risk of hospital readmissions (Mantzourani *et al.*, 2020). During the Covid-19 pandemic, the DMR was the only advanced service that the Welsh Government chose to continue within community pharmacies, recognising its ability to reduce pressure on NHS services (Welsh Government 2020). However, the DMR and other

initiatives do not usually provide clinical reasons for changes to a patient's medicine while in hospital and unlicensed 'special medicines are often initiated in secondary care by specialist consultants with no clear established pathway to provide the justification and clinical need to prescribers and community pharmacists in primary care.

The need for clinical information to be made accessible for community pharmacists has been recognised in the literature and has been suggested as a potential method of improving continuity after discharge, but is not regularly employed within the healthcare system (Urban *et al.*, 2013). Although evidence has suggested that community pharmacy staff are in a realistic position to assist patients during transfer of care (Kooyman and Wiltry 2019), and that providing community pharmacy staff with insight and input into full patient records would allow informed decisions to be made and increase patient safety (The Pharmaceutical Journal 2019), the relationship between GPs and community pharmacists is reported in the literature as suboptimal (Hindi, Jacobs and Schafheutle 2019).

This lack of information was highlighted by participants in this study as a factor that reduced their perceived confidence, however the participants also described multiple factors that helped to increase their confidence even when a lack of information was received with prescriptions. Participants perceived the hospital prescribers to hold specialist knowledge and experience, and this perception led to an increase in trust felt towards them. This trust was seen to reassure participants, reduce concerns and increase confidence in their role of supplying unlicensed 'special' medicines to patients. Professional trust is an important aspect when working as part of a healthcare team and has been reported previously within the literature (Frankel and Austin 2013). Although this professional trust was seen to increase participants' confidence in supplying unlicensed 'special' medicines, the lack of information received and the methods community pharmacy staff had to take, such as contacting prescribers and reviewing evidence about the medicines increased the workload within the pharmacy. It is also noted that the professional trust described by participants towards primary and secondary care prescribers and even towards the suppliers was a result of a need to trust others in the supply chain. Without the specialist knowledge of prescribers, or suppliers, it is difficult for community pharmacy staff to assess the suitability of unlicensed medicines, especially if the medicine is unusual or uncommon, despite sharing the legal responsibility for the use of the medicine (RPS 2015). In this way community pharmacy staff almost have to rely on this element of professional trust as they may not have specialist knowledge about the medicine prescribed but would still be liable for any harm that the medicine has caused to a patient.

The results suggest that in order to increase confidence and streamline the process for community pharmacy staff obtaining and supplying unlicensed 'special' medicines, there is a clear need for integration and an established pathway for patients receiving these medicines across care settings. Integrated care aims to improve patient outcomes by streamlining the processes across care settings and making them more efficient (Shaw, Rosen and Rumbold 2011). Integrated care pathways outline and detail what should happen at different stages of the patient journey and are used in the UK for a range of conditions (Campbell *et al.*, 1998). The use of integrated care pathways has been found to be beneficial in a number of ways, including improving clinical outcomes (NCPNW 2006), encouraging interprofessional teamwork, and can result in an increase in communication and healthcare professional knowledge (Scaria 2016). Integrated care pathways can also play a valuable role in determining recommendations for change to improve services (Baron 2009).

Due to the lack of an established care pathway and the transfer of responsibilities from prescribing clinicians in secondary care to general practitioners and community pharmacists to share in primary care (RPS 2015), this leaves areas where the continuity of treatment could be interrupted. Participants highlighted how the perceptions of this responsibility had been seen to lead to delays or disruption, with GPs deciding not to continue prescriptions. The awareness of other healthcare professionals was also seen to impact the continuity of supply with GPs accidentally prescribing unlicensed 'special' medicines. These issues have also been reported elsewhere in the UK with GPs being unwilling to continue prescriptions for unlicensed 'special' medicines citing reasons such as cost, a lack of available evidence, and a lack of personal experience (Wong *et al.*, 2006).

The issues experienced by participants in this study and described above support the need for an established integrated care pathway when supplying unlicensed 'special' medicines. One participant suggested that by incorporating a standardised template with clinical information which could accompany prescriptions for unlicensed 'special' medicines across the care settings, this would help to increase the confidence felt by primary care staff and would help to reduce the workload within the pharmacy when receiving prescriptions.

Another factor that was highlighted to impact participants' confidence was the previous experience each participant had had within the role of procuring and supplying unlicensed 'special' medicines. Participants described how the more time they had spent within the role, the more their confidence had grown in general and this included sourcing, acquiring, and supplying unlicensed 'special' medicines. Participants with more experience still acknowledged challenges with finding information about unlicensed 'special' medicines and sourcing new prescriptions, but were more confident in their abilities to do this, and in the

outcomes of supplying unlicensed 'special' medicines to patients. This experience of community pharmacy staff building their understanding around unlicensed 'special' medicines from within their role is supported by the literature (Stuart *et al.*, 2007), this is because Undergraduate Pharmacy curricula do not typically focus on how to use unlicensed 'special' medicines due to its complexity (GPC 2011). Increasing professional development around the use of unlicensed 'special' medicines could be provided by existing national institutions for example Higher Education England (HEE) and Health Education and Improvement Wales (HEIW) which would help to improve the consistency of information being supplied to healthcare professionals and increase the confidence felt.

Apart from the issues caused by a lack of awareness in patients of the licensing status, understanding of what unlicensed medicines are, or the lack of a clear established pathway to share clinical information, participants described some practical factors that were seen to impact the continuity of supply. The use of an online ordering system was reported to improve continuity by reducing the workload involved in ordering unlicensed 'special' medicines and improved the efficiency of communication with suppliers. The literature has previously reported how technology can be successfully integrated within community pharmacies (Goundrey-smith 2014) and the beneficial impact this can have on patient care (Pettrakati *et al.*, 2011, Mantzourani, Way and Hodson 2017). However, some participants within this study were still using outdated forms of technology when ordering unlicensed 'special' medicines such as fax machines, despite the security risks and expenses associated with their use (The Pharmaceutical Journal 2017). The results of this study suggest that community pharmacies may benefit from using an online ordering system and upgrading technological equipment where practical.

#### **4.6.1 Limitations**

As the study was conducted using a limited census from one small chain of community pharmacies in South Wales, the results gained are not generalisable to other chains or community pharmacies. However, the results provide an insight into community pharmacy staff views and experiences in Wales when obtaining and supplying unlicensed 'special' medicines and form the base for developing a survey to be used in future research.

There is also the potential for bias in the recruitment process as the participants' employer, who partly funded the project, could essentially be aware of who participated. In order to minimise this, it was agreed that the researcher would not share any raw data or personal identifiable information from the participants with the head of the company.

## 4.6.2 Reflections

The researcher experienced the benefit of having a SSG in the design of the study methods and the interview schedules. The suggestion given by the SSG to include a question about SOP's helped the researcher to better understand the process within the community pharmacy. The researcher gained valuable experiences and an improved understanding while talking to this sample population about how unlicensed 'special' medicines are accessed and supplied in the community. The discussions allowed the researcher to gain an insight into the current challenges experienced when accessing and supplying unlicensed 'special' medicines.

Upon reflection, the researcher would have liked to have gained a larger sample of community pharmacists from a variety of chains and independent pharmacies to produce more reliable results across a wider geographical area. However, the results from this study support findings of previous studies which helps to validate the results and highlights important issues that are still ongoing. As qualitative methods are focussed on gaining more individual results than simply generalisable results, despite the small sample size gained the researcher believes each participant's views and experiences are important, valuable and help to add to the existing literature in this area.

## 4.6.3 Conclusions

The results of this study give the first insight into the views and experiences of community pharmacists' and pharmacy technicians' when accessing and supplying unlicensed 'special' medicines in Wales. A unique finding of this study was the fact that community pharmacy staff described a need to 'train' patients to ensure they could effectively manage the extended lead times experienced when accessing unlicensed 'special' medicines.

Participants described the important role patients play when accessing and supplying unlicensed 'special' medicines and explained how their own confidence to supply these medicines varied depending on the medicine itself, the information available and their individual experiences. Issues were reported that were seen to delay the continuity of supply; however, the use of an online ordering system was described as a benefit to pharmacy staff helping to streamline the process of ordering unlicensed 'special' medicines. The lack of awareness of what unlicensed 'special' medicines are, and the limited confidence highlighted across healthcare professionals when obtaining and supplying unlicensed 'special' medicines suggests a need for further education in this area and an integrated care pathway to reduce the risks of disruption seen across care settings.

#### **4.6.4 Using the results for further research**

The results gained from this study were used to create a survey tool which could be further adapted or used within further research, to explore the views and experiences of community pharmacy staff on a larger scale. Using a survey in this way would require the use of quantitative methods. The following section will outline the use of quantitative methods, including the different types of surveys that could be used, the methods of administration, techniques to improve response rates and a description of how the survey tool was designed.

##### **4.6.4.1 Quantitative methods**

The two main approaches used when conducting quantitative research are experimental or non-experimental designs (Quick and Hall 2015). Experimental approaches typically involve testing a hypothesis and manipulating independent variables to determine causal relationships and effect on a dependent variable (Kirk, 2012). Non-experimental descriptive methods typically use surveys or questionnaires. Surveys and questionnaires are commonly used within health research (Schofield and Knauss 2010), and can be used to collect information about a specific group of people, their experiences, behaviours, and beliefs (Moser and Kalton 2017). Surveys used within non-experimental studies include cross-sectional and longitudinal. Cross sectional surveys are carried out only once and gain information from a specific point in time (Larson 2017). These surveys are useful for exploring the current thoughts or behaviours of individuals, for example understanding the effect of internet use in healthcare professionals (Podichetty et al., 2006), or assessing the knowledge and attitudes around antibiotic use (Scaioli et al., 2015). However, cross-sectional surveys do not usually explore topics in detail in terms of meaning for the participant and cannot demonstrate changes overtime (Connelly 2016).

Longitudinal surveys are carried out with the same sample but on multiple occasions (Lynn 2009). By gaining data over years or even decades, longitudinal surveys are often used to understand patterns between disease and risk factors or treatment outcomes (Caruana et al., 2015). However, as participants are required to complete the survey on multiple occasions this increases the burden on participants (Laurie and Lynn 2009) and also the time and cost needed to conduct the survey (Rindfleisch 2008).

As the research aimed to gain the views and experiences of participants around the use of unlicensed 'special' medicines and how accessible or acceptable they are perceived to be at a specific point in time, cross-sectional surveys would be more appropriate.

#### **4.6.4.2 Methods of administration**

Surveys can be administered in a number of ways including in person, over the phone, through the mail or online. In person surveys allow complex information to be presented to participants however conducting each survey in person is costly (Marta-Pedroso, Freitas and Domingos 2007). Telephone surveys have been found to be a low-cost substitute to in person interviews (Aneshensel 1982), however they do not allow for more complicated questions where participants are required to see or read something (Wright and Marsden 2010) and are still more time consuming than other methods such as online surveys (Braunsberger 2007). Surveys that are sent through the mail benefit from being an affordable and efficient method of administration and allows for wider coverage geographically, however this method is typically recognised to return low response rates (Bourque and Fielder 2003) and can be more costly than other methods (Cobanoglu, Moreo, and Warde 2001). Lastly, online surveys offer an efficient and cost-effective method of reaching a large number of participants, potentially globally, however they tend to have lower response rates and rely on participants ability to access the internet (Evans and Mathur 2005).

All survey methods have advantages and disadvantages and as the studies in this thesis are looking to gain the views and experiences of participants across Wales, mail and online methods of administration would be the most suitable.

#### **4.6.4.3 Techniques to increase response rates**

There are multiple factors that can affect the response rates when researching using surveys, in order to improve response rates in mail and online surveys certain strategies have been developed. Some initial considerations described in the literature were the use of multiple reminders, the use of incentives (Nulty 2008). This involved sending repeat email reminders to students who could participate and to the owners of the survey such as academic staff and offering prizes that could be won for participation as part of a draw. The evidence showed that the survey response rate was highest when using all methods together, however the studies included were focused on surveys conducted with students in University and so may not be generalisable to surveys conducted with the public. In 2013 Cho, Johnson and VanGeest conducted a meta-analysis where multiple strategies to improve response rate in clinicians were reviewed across 48 studies. The results showed that response rates were highest for mail surveys compared to online or mixed surveys. Higher response rates were also seen when monetary incentives were provided compared to non-monetary incentives or no incentives. The use of follow ups were also reported to increase response rates, when one or two follow-ups were used.

#### **4.6.4.4 Survey tool design**

A survey tool was designed using the themes generated above and framing questions around these findings (see Appendix 9). By using the results already gained the survey could be used to determine if the findings are supported by a larger sample of community pharmacy staff members. The researcher designed a draft of the survey tool based on the results gained from study 1, this drafted survey tool with the topic guide was then sent to members of the SSG and feedback was provided. The researcher updated the survey tool using the SSG feedback in multiple ways including editing its structure and order, and adding in specific response options to gain more detailed responses. For example, instead of asking if the pharmacist was working at an independent pharmacy or a chain, to provide defined options specifying the number of sites to distinguish between small chains and large chains. The researcher recognises the survey tool has not been validated or piloted, which would need to be completed before being disseminated across Wales, but could be adapted for further research.



## **5. Study 2 - Semi-structured interviews with patients/parents and carers**

### **5.1 Overview of chapter**

The previous study chapter explored how unlicensed 'special' medicines are acquired and supplied by community pharmacy staff in Wales. Study 2 focusses on understanding the views and experiences of patients, or the parents and carers of patients who access and receive unlicensed medicines. This chapter will consist of a brief introduction to the research topic, including some background information about what has already been reported in the literature and the justification for the research aims. The aims and objectives will be clearly outlined.

Following this, a detailed look at the ethical review and approval process will be provided, along with a description of the specific methods used to explore the views and experiences of patients or the parents and carers of those receiving unlicensed 'special' medicines in the community in Wales. Details of the sampling and recruitment strategy will be described followed by an explanation of how data was collected and analysed along with the ethical considerations for participants. After this, the results of semi-structured interviews will be provided, starting with information about the sample gained, and followed by an in-depth look at the results of the analysis. Each theme and sub-theme identified will be described in detail and anonymised quotes will be provided directly from the interview transcripts to support the findings of the analysis. Lastly, a discussion exploring the findings of the study will be presented in the context of the existing literature and this will be followed by a description of the study limitations, the researcher's reflections, and the final conclusions.

### **5.2 Introduction**

As detailed in chapter 1, in certain scenarios the use of licensed medicines may not be suitable and in these cases an unlicensed medicine can be supplied to meet the clinical needs of the patient (MHRA 2014a). Patients have the final responsibility when receiving prescription medicines to ensure they collect their medicines when required and adhere to the treatment schedule recommended.

As highlighted in the introduction and systematic review chapters (see chapter 1 and 2) there is little known about the views and experiences of those who receive unlicensed 'special' medicines in the UK, specifically in Wales. The available literature from within the UK has highlighted that patients have experienced issues when accessing their unlicensed medicines after discharge (Wong *et al.*, 2006), and that patients receiving unlicensed

'special' medicines in the community are required to take on additional responsibilities to ensure continuity, such as informing the community pharmacy in advance of when further supplies are needed (see chapter 4), and increased communication with healthcare professionals (Husain, Davies and Tomlin , 2017).

Some patients may have an unlicensed medicine initiated in primary care while others may first receive an unlicensed medicine in secondary care and later have their care transferred into the community. As the previous literature highlighted issues during transfer and receiving unlicensed medicines in the community, the study aimed to explore the views and experiences of patients receiving unlicensed medicines. Participants were recruited directly from primary care or were provided with information about the study just prior to being discharged from secondary care in which they were informed that they would be able to participate when they had collected their unlicensed medicine from a community pharmacy at least once (see Appendix 6).

Despite evidence from within the UK, to the researcher's knowledge, there are no studies exploring the views and experiences of patients specifically in Wales, where patients are not required to pay for prescription medicines (Welsh Government 2017a). In order to make evidence-based suggestions to improve the patients' experience, as the overall thesis aims to do, it is important to understand the views and perspectives of those who receive unlicensed medicines. By obtaining an insight into the views and perceptions of those who receive unlicensed medicines within Wales, factors affecting the patient journey and successful treatment can be identified and used to generate recommendations for change, while supporting previous evidence or identifying findings specific to patients in Wales.

### **5.2.1 Study 2 aims and objectives**

The aim of study 2 was to explore the views and experiences of patients, or the parents and carers of those who receive unlicensed 'special' medicines in the community.

#### **Objectives:**

- To investigate patients' understanding of unlicensed 'special' medicines and their use in practice;
- To explore patients' perceptions of safety and quality of unlicensed 'special' medicines from different sources;
- To investigate patients' experiences around receiving unlicensed 'special' medicines, manufacturing timelines and delay obtaining treatment.

## 5.3 Ethical approval process

The project was funded by the Knowledge Economy Skills Scholarships (KESS 2), with contributions from an unlicensed 'special' medicines manufacturing unit. As the study involved participation from patients who are under the remit of NHS ethics, a review of the study and approvals were needed from a Research Ethics Committee (REC), and full approvals were also required from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW). A timeline of the ethical approval process for this study can be seen in table 3.1.

The ethical approval process began by applying for sponsorship from Cardiff University which was gained on the 6<sup>th</sup> August 2019. Following this, an application was submitted to the NHS through the Integrated Research Application System (IRAS) on the 23<sup>rd</sup> August 2019, the application was given the IRAS number: 268899. This consisted of a 125-page application, containing the IRAS application, the project protocol, copies of all the supporting documents and copies of the interview schedules. The application was put forward for proportionate review at the North West - Liverpool Central Research Ethics Committee and was given the reference number: 19/NW/0598. A favourable opinion was given with conditions on the 4<sup>th</sup> September 2019, conditions included clarifying how gatekeepers would be identified for each study, and how information would be stored and transferred throughout the research process. The conditions and comments received were addressed and the protocol and supporting documents were updated and uploaded to the IRAS on the 25<sup>th</sup> September 2019 with full HRA and HCRW approval being gained on the 23<sup>rd</sup> December 2019.

After full NHS ethical approvals had been received, local information packs and research passport application packs were created and sent to each health board. At this point individual health board facilitators contacted the researcher directly and provided information about how the study would be set up if approved by the health board. As part of the process, some health boards chose to assess the project for capacity prior to processing the research passport application pack, while others suggested that capacity and passports would be approved and sent out at the same time. This resulted in different stages of progress for approval within each health board, meaning recruitment had to be staggered while awaiting the letter of access from each health board. Letters of access were gained from six health boards, the individual dates these were received can be seen in table 3.1, details of the non-substantial amendments submitted over the research process can be seen in Appendix 8. All amendments were approved by the REC and provided to individual health boards. During the registration of the study, the researcher contacted the health board facilitators who had

received and responded to the local information packs and research passport application packs and asked for help in identifying potential gatekeepers, within specific departments (see 5.4.2.3).

## **5.4 Methods**

Patients who receive unlicensed 'special' medicines may do so for a number of reasons to treat a large range of conditions and have individual clinical needs that need to be met, as such it was anticipated that patients would have largely differing views and experiences related to these medicines. As described in the previous chapter, in order to explore and better understand each participant's individual experience, a constructivist research paradigm with a qualitative phenomenological approach was selected (see chapter 3.2 and 3.3), which involved the use of semi-structured interviews (see chapter 4.4). In this way the individual participant's subjective reality could be explored and attained, while allowing their own perceived issues of importance to be raised.

### **5.4.1 Data collection materials and technologies**

The researcher, after gaining feedback from the steering group (see chapter 3.6) created an interview schedule for patients or the parents and carers of those who receive unlicensed medicines. The interview schedule aimed to explore patient views and perceptions around the use of unlicensed medicines and the questions were created and structured to allow patients to outline their individual journey from first receiving a prescription for an unlicensed medicine, to receiving their medicine in the community. All participants were interviewed using the same interview schedule regardless of whether they had been recruited from primary or secondary care. As the methods used to recruit patients from within primary or secondary care varied (see 5.4.2.2. and 5.4.2.3) the study documents created differed slightly. Individual cover letters were created for gatekeepers within the different care settings and reminder stickers were provided to community pharmacy staff that could be placed on medicine bags to remind staff to provide patients with the study materials. However, all patients were supplied with the same study materials which included a study advert, an information booklet and a prepaid envelope. Participants were also given a consent form after they had expressed an interest to take part in an interview. The information booklet contained a participant information sheet which outlined the details of the study and how the participants could be involved. The cover page of the information booklet can be seen in figure 5.1 and all the study materials, including the full information booklet, can be seen in Appendix 6. All information created for patients were translated into Welsh using a translation service within the University and supplied alongside the English version.

Interviews were conducted and recorded using Microsoft Teams, a laptop and NVivo qualitative data analysis software (QSR International Pty Ltd. Version 12. 2018) were used during the initial transcription and analysis.

Version 4 Jan 2020



## Are you or someone you care for using unlicensed “special” medicines?

Join us in a study to discuss your experiences and what further support you would like!



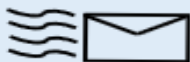
### What will I have to do?

Attend an interview to discuss how you obtain your special medicines and any problems you have

### Will I be compensated?

You will receive a £15 High street voucher for taking part in an interview.

££



### What should I do now?

Answer the questions in the back of this booklet and send us your replies using the pre-paid envelope. We will be in touch as soon as possible!

Research approved by North West -Liverpool Central Research Ethics Committee ref no. 19/NW/0598

Participant Information Booklet

**Figure 5.1** Patient information booklet cover page

#### **5.4.1.1 Interview schedule development**

The researcher began by using the information gained from the available literature and discussions with stakeholders to create an interview schedule for patients. The interview schedule for patients focussed on the processes involved and experiences of accessing and receiving unlicensed medicines. Feedback on the interview schedule was gained from the SSG and the assistant head for the NHS specialist pharmacy service. Recommendations for change were discussed with the supervisors and incorporated into the final version of the interview schedule. An example of a change made to the interview schedule using the SSG feedback was the inclusion of a question asking patients if their medicine had been reviewed at any point and if subsequently any changes had been made to their prescription. The researcher had also created some questions with prompts for patients who had originally received their medicine from secondary care and those whose treatment had been initiated in primary care. After gaining feedback, the format of these questions were edited to create one specific question asking about transition of care that could be asked only to patients who had experienced this, to ensure the remaining questions were relevant to all participants. Once finalised, the interview schedule created focussed on four main areas, the process involved in having been prescribed a special, accessing the medicine during transfer of care from secondary care to primary care, or directly from primary care, the impact of the medicine and the experiences with the community pharmacy.

#### **5.4.1.2 Impact of Covid-19 on data collection materials**

Due to the Covid-19 restrictions and logistic difficulties accessing post during the start of lockdown, a booklet insert was also provided to potential participants as part of the information booklet, which outlined the option for them to respond to the researcher through email and to send images of the completed questions and consent form prior to arranging an interview. In order to do this, the researcher submitted a non-substantial amendment to the REC about the inclusion of the booklet insert to provide this option to potential participants (see Appendix 8).

#### **5.4.2 Sampling and recruitment strategy**

The sampling frame included patients (parents/carers of patients) who were currently being prescribed an unlicensed 'special' medicine and were receiving this in the community in Wales. Potential participants were identified using stratified, purposive and convenience sampling. Individuals with the ability to give informed consent aged 16 years and over became the sample population.

There is no statute in the UK that governs a child's right to consent to participating in research, however common law suggests that individuals between the ages of 16-18 are

usually competent to give consent to treatment (HRA 2018), and in the British court system, 16-17 year olds are classed as young people and are able to give consent (Parker 2018). As such, it is presumed that young people are also competent to consent to take part in research. In this case where the potential risks were small, participants identified between the ages of 16-17 would have been invited to take part in the interview independently.

If someone had difficulty with communication or was incapacitated in some way, a carer responsible for collecting the individual's prescription would be asked to provide consent and take part in the interview (it was the individual patient's choice if they wanted to be present at the time of the interview but would also need to provide written consent if attending). The inclusion and exclusion criteria can be seen in table 5.1. Participants who met the inclusion criteria became the sample population.

**Table 5.1** Inclusion and exclusion criteria for participants in study 2

Eligibility criteria	Patient/Guardian/Carer
<b>Inclusion criteria</b>	
<b>Population</b>	<ul style="list-style-type: none"> <li>• Individuals or carers/parents of individuals who have been initiated or on maintenance therapy with an unlicensed 'special' medicine;</li> <li>• Individuals who access unlicensed 'special' medicines through a community pharmacy, (as new or maintenance therapy) or will be discharged from secondary care and have been initiated on an unlicensed 'special' medicine;</li> <li>• Over the age of 16.</li> </ul>
<b>Experiences</b>	<ul style="list-style-type: none"> <li>• Individuals who have been initiated or on maintenance therapy with an unlicensed 'special' medicine in primary or secondary care;</li> <li>• Individuals who have accessed an unlicensed 'special' medicine from a community pharmacy at least one time.</li> </ul>
<b>Communication</b>	<ul style="list-style-type: none"> <li>• Can communicate effectively in English (does not have to be first language), to be assumed upon response to the information booklet;</li> <li>• Ability to provide informed consent.</li> </ul>
<b>Exclusion Criteria</b>	
<b>Population</b>	<ul style="list-style-type: none"> <li>• Individuals or carers/parents of individuals who require and have current prescriptions for licensed medicines only;</li> <li>• Under 16 years of age.</li> </ul>
<b>Communication</b>	<ul style="list-style-type: none"> <li>• Unable to provide consent.</li> </ul>

As the study involved recruiting patients from within secondary care (who were due to be discharged and to continue to receive their medicine in primary care) and patients who had been receiving their medicine within primary care, participants were recruited using a range of methods which are outlined below:

### 5.4.2.1 Recruiting patients online

HealthWise Wales is an online platform with a register of members of the public who have agreed to be informed about research (Hurt *et al.*,2019). With over 40,000 participants registered, the organisation aims to assist recruitment by advertising studies directly to a large cohort of members of the public across Wales (HealthWise Wales 2021). The researcher contacted the HealthWise Wales team, who agreed to disseminate a newsletter through email that included the researcher's study advert to their members across Wales. The study advert can be seen below (figure 5.2) and can also be found in Appendix 6. The study was advertised by HealthWise Wales on two separate occasions and adverts were also placed by the researcher and academic supervisor on social media accounts such as Facebook and Twitter in an attempt to recruit participants online. If any potential participants were interested in taking part, they were instructed to contact the researcher directly. When contact had been made the researcher sent the potential participant the study information to determine eligibility and arrange a time to participate in an interview.

Version 2. Jan 2020.



**Research into unlicensed medicines**

**Are you, or someone you care for, using unlicensed 'special' medicines? Would you consider spending 10-20 minutes of your time to help improve the care and support you receive?**

Many patients need an unlicensed 'special' medicine to treat their condition. Unlike licensed medicines, unlicensed 'special' medicines can sometimes be harder to access and riskier to take. There is little known about the views and experiences of the patients who receive unlicensed 'special' medicines in Wales, or of the processes they use to do this.

In Cardiff University, we are conducting a study to explore the views and experiences of patients who receive unlicensed 'special' medicines. The study will involve completing a small survey and taking part in a short interview. Interviews are expected to last between 10-20 minutes and will be held at a time and location of convenience to the participant. Anyone who participates in the interview will receive a **£15 high street voucher**.

If you would like more information, or to find out if you are eligible and would like to take part in this study, please contact Miss Alesha Wale at [Walea1@cardiff.ac.uk](mailto:Walea1@cardiff.ac.uk) or on 07564247000.

**Figure 5.2** Unlicensed medicine study advert



#### **5.4.2.2 Recruiting patients from within primary care**

The researcher was given access to the dispensing data for unlicensed 'special' medicines for the year 2018 (Mantzourani 2019), which was used as a basis to stratify community pharmacy premises for recruitment purposes. The researcher began by splitting the data by health board. The researcher originally planned to take the six highest dispensing pharmacies from within each health board however, this left the sample bias towards chain pharmacies and meant sites within the same company were identified in each health board. In the hopes of producing a more representative sample, the researcher decided to select four of the highest dispensing chain community pharmacies and two of the highest dispensing independent community pharmacies, with no chain being selected more than three times across all health boards.

Once the list of community pharmacies had been selected, they were first approached by a gatekeeper working with Community Pharmacy Wales. This gatekeeper then contacted the researcher with lists of which community pharmacies had expressed an interest in getting involved. The researcher reached out to the pharmacy site, providing further details about the study, what it would involve for the pharmacy staff and asked for an estimation of how many booklets they would require.

The researcher provided the pharmacies with copies of the patient information booklet, prepaid envelopes and reminder stickers through the post. The selected gatekeepers within the pharmacies were given a cover letter outlining what they would be required to do. This included identifying when unlicensed 'special' medicines were to be dispensed, placing the information booklet and prepaid envelope into patients' medicine bags, and giving them a brief outline of the research topic and what it would involve if the patient decided to take part. At no point did the researcher have access to any patient medical records. One month after this, gatekeepers were asked to remind patients receiving unlicensed 'special' medicines about the research and were offered extra copies of the information booklet, if needed. If potential participants did not respond after this point it was assumed that they did not wish to take part in the study and no further contact was made by the gatekeepers to recruit participants on behalf of the research team. In this way a combination of stratified, purposive and convenience sampling was used to recruit potential participants from within primary care.

#### **5.4.2.3 Recruiting patients from within secondary care**

The researcher was informed by stakeholders in the SSG that specific clinical areas were more likely to be using unlicensed 'special' medicines than others, these were paediatrics, dermatology, and gastroenterology. The researcher aimed to recruit patients within these

areas who would be discharged and transitioning into the community, so as to better understand and explore the experience of transitioning between care settings when receiving an unlicensed medicine. Purposive and convenience sampling was used to recruit potential participants from secondary care.

Recruitment took place in a number of ways involving the researcher contacting the individual health board facilitators, as identified during the registration process (see 5.3) and asking for contacts within the specified departments who could act as gatekeepers to be identified. Different health boards had different approaches to this: some health board facilitators agreed to disseminate the information directly to individuals within the required departments, while others provided contacts for the researcher to reach out to directly. Where the health board facilitator agreed to disseminate the study information, the researcher sent the study information directly to them to be disseminated to potential gatekeepers. Where contacts were provided, the researcher then contacted the individuals and sent them the study information asking them to act as a gatekeeper for the study.

The researcher and academic supervisor had also made contact with a clinical reader and consultant dermatologist who was involved in organising academic meetings for a group of dermatologists from across South West Wales, prior to the start of the study. Once full approvals had been gained, the researcher attended a monthly meeting and presented potential participants with information about the research. Potential participants were invited to act as gatekeepers in recruiting patients. All gatekeepers were asked to re-send the study information to potential participants after one month, if potential participants had not contacted the researcher after this point, it was presumed they did not want to take part and no further contact was made to recruit them.

All participants from within primary and secondary care were provided with the same information (see 5.4.2.1) and were self-selected. Patients (and parents/carers of patients) were asked to complete some short questions (within the information booklet) providing some descriptive information and to send it to the researcher in the prepaid envelope supplied. The questions aimed at giving the researcher some baseline data on the medicines used and allowed participants to participate further in the study by expressing interest in taking part in an interview. The researcher used the answers provided by patients to begin the interview and to break the ice by confirming some of the information they had provided. The simple questions answered by the participants were also used by the researcher to look up the medicines received before the interviews, to better understand the patients' conditions, as the researcher is not a pharmacist and was not familiar with the individual medicines or their uses. Once the completed questions were received by the

researcher, those who expressed interest in taking part in an interview and provided contact information were contacted for the first time directly by the researcher. A suitable time was arranged to conduct the interview. Once the interview had been completed all participants were sent a £15 high street voucher through the post for taking part. Recruitment took place from August 2020 until June 2021 (see also section 5.4.2.4 Impact of Covid-19 on recruitment).

#### **5.4.2.4 Impact of Covid-19 on recruitment**

The restrictions enforced during the Covid-19 pandemic resulted in the postponement of research in March 2020, meaning recruitment could not be started until August 2020. The re-start date of recruitment varied between health boards, causing a significant delay in the recruitment period. Prior to the Covid-19 pandemic, the researcher had aimed to recruit a total of 10 patients within each health board selected, however as a result of the delays caused, the target sample sizes were reduced. To combat the delays and disruption experienced, the researcher also applied to extend the project, and this was approved for an extra 4.5 months. A timeline of the ethical approval process for this study can be seen in table 3.1.

#### **5.4.3 Setting**

Interviews with patients were originally planned to be held in public locations such as libraries, community centres or cafes, and conducted over the phone or online virtually, allowing the participant to choose the method most suitable for them.

##### **5.4.3.1 Impact of Covid-19 on setting**

Due to the timing of the Covid-19 pandemic and the social distancing restrictions enforced, no interviews were conducted in public locations and instead all interviews were conducted remotely to ensure that data collection did not involve physical contact with participants. Patients (and parents/carers of patients) who received unlicensed 'special' medicines were interviewed virtually online using Microsoft Teams, this allowed all willing members of the sampling frame to take part in an interview from home.

#### **5.4.4 Ethical issues pertaining to subjects**

There was a small potential risk that participants may have become upset when discussing sensitive information related to their health or the health of their children and patients they care for. To target this, participants were encouraged to ask questions before and after taking part in the interview and were given the researcher's and the academic supervisor's contact details to allow them to discuss the project or address any concerns they may have had at any time.

### **5.4.5 Data collection methods**

Data was collected using a semi-structured interview, once the researcher had received the signed consent form, a suitable time to conduct the interview online was arranged directly with the participant at a time of their convenience. All participants were given the opportunity to ask questions before and after taking part in the interview. The researcher made notes during the interview of any visual responses such as head shaking or nodding and facial expressions. All interviews were conducted and recorded online using Microsoft Teams to ensure an accurate transcript could be created while allowing the researcher to pay complete attention to the participant. The recruitment and data collection period started in August 2020; data was first collected for this sample in November 2020 and continued until June 2021.

### **5.4.6 Data processing**

The data processing methods are consistent with methods described in study 1 outlined in chapter 4 (see chapter 4.4.6).

### **5.4.7 Data analysis**

The data analysis methods are consistent with methods outlined in chapter 4 (see chapter 4.4.7).

## **5.5 Results – Interviews with patients/parents and carers**

### **5.5.1 Participant characteristics**

A total of four participants took part and completed an interview, two were patients receiving unlicensed medicines themselves and two were parents accessing unlicensed medicines for their child. As gatekeepers were involved in disseminating study information to patients across settings, the total number of potential patients invited to participate is not known and therefore the response rate cannot be accurately determined. The semi-structured interviews conducted lasted between 20-40 minutes. Participant demographics can be seen in table 5.2. This includes the interview number given to each participant, the age and gender of the patient receiving the medicine, the name of the unlicensed 'special' medicine received, the number of community pharmacies used to obtain a supply of the medicine, the number of years the medicine has been received, and who the medicine was first initiated by.

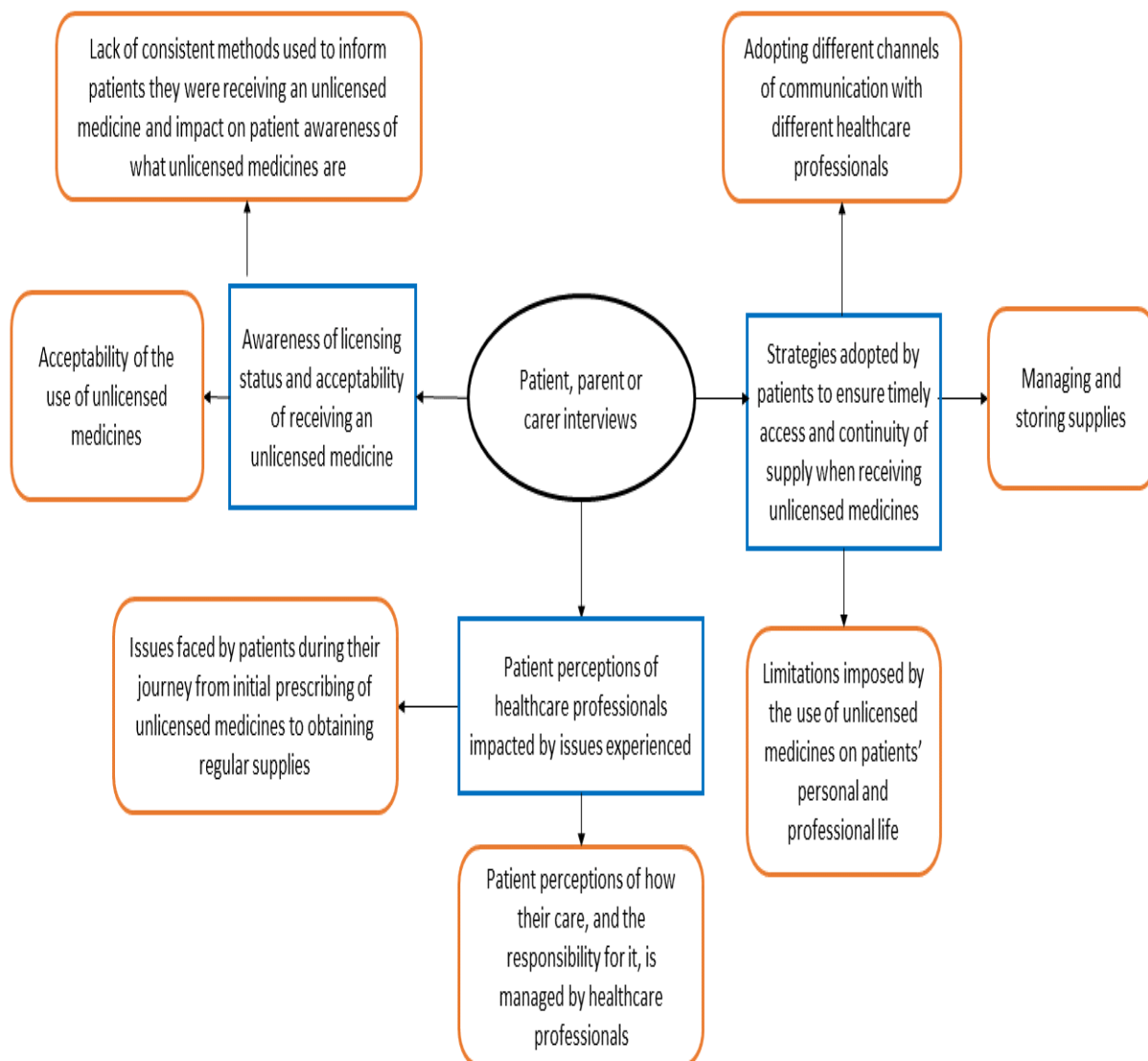
**Table 5.2** Study 2 participant demographics and unlicensed medicines received

Interview/ participant number	Age of patient (years)	Gender of patient	Unlicensed medicine received (specific dose not recorded)	No of community pharmacies used to access the medicine	Years receiving unlicensed medicines	Medicine first initiated by
2.1	32	Female	Liothyronine sodium - Treatment for autoimmune thyroiditis - Dose twice a day (Tablet)	1	9 yrs	Private doctor
2.2	67	Female	DHEA and testosterone Hormone treatment	1	1 yr 2 months	Private doctor
2.3	9*	Male	Spironolactone – Treatment for reduction of fluid build-up - Oral suspension	1	5 yrs	Hospital doctor
2.4	14*	Male	Glycopyrronium – Treatment for hypersalivation. oral solution (2.5mls four times a day, but dose given varies depending on need)	1	12 yrs	Hospital doctor

\*Where the age of the patient was under 18 years, the parent or carer was interviewed on their behalf

### 5.5.2 Thematic analysis results

Reflexive thematic analysis of transcribed interviews was used to construct three themes: (1) awareness of licensing status and acceptability of receiving an unlicensed medicine; (2) patient perceptions of healthcare professionals impacted by issues experienced; and (3) strategies adopted by patients to ensure timely access and continuity of supply when receiving unlicensed medicines. A graphic representation of the themes and sub-themes can be seen in Figure 5.3.



**Figure 5.3** Themes and subthemes constructed through thematic analysis of semi-structured interviews with patients, parents or carers

### 5.5.2.1 Theme 1 – Awareness of licensing status and acceptability of receiving an unlicensed medicine

Participants reported differences in how they were informed they were being prescribed an unlicensed ‘special’ medicine, with some being given information leaflets containing information about unlicensed medicines and one participant not being informed at all despite receiving the unlicensed medicine for many years. This variation in what and how they were informed was reflected in the range of definitions provided by patients. The acceptability of unlicensed medicines was reported to be influenced by factors such as if the medicine was

off-label or an unlicensed 'special' medicine, with the word 'unlicensed' causing concern, however this concern was mitigated by the patients' perceptions of need. The perception of need was also described to outweigh concerns about the potential risks of using unlicensed medicines and all participants reported positive outcomes of taking their medicine, further reinforcing the need for their use and reducing concerns around risk.

#### **5.5.2.1.1 Lack of consistent methods used to inform patients they were receiving an unlicensed medicine and impact on patient awareness of what unlicensed medicines are**

Participants reported differences in how they were informed their medicine was unlicensed with some being told prior to being prescribed the medicine that it was unlicensed and provided with some information about what this meant.

*“Oh yes, yes, yes, [the prescriber] explained that [the medicine was unlicensed], and she gave me a leaflet explaining what... unlicensed medicines are” [INT 2.2].*

One participant however was not aware they were receiving an unlicensed 'special' medicine until they were invited to participate in this study by their community pharmacy team. The participant acknowledged that the medicine had to be ordered into the pharmacy but described how they took this only to mean the medicine was not in stock and outlined that nobody throughout their healthcare journey had specified the licensing status of the medicine with them.

*“It's literally only from you [the invitation to the study] that I realised it's unlicensed, there was all- you know, I could give them [the pharmacy] the prescription, and I'd always know that it would have to be ordered, so I'd say I'll pick it up in a couple of days, but no one ever mentioned that it was unlicensed, I just assumed it wasn't something they had in stock, so they'd have to just order it, I didn't know that was why” [INT 2.3].*

This lack of consistent approach in informing patients led to participants not having a clear understanding of what an unlicensed medicine is, giving varying definitions with some describing medicines that are not approved in the UK and others just describing the need to order the medicine into the pharmacy.

*“What I think, [an unlicensed 'special' medicine is] it has not been approved in UK, but still if, someone needs it, doctor you know, loads of doctors review it, it's not, you know won't do any harm, they'll just help that person you know they will prescribe it” [INT 2.4].*

Two of the participants expressed their understanding of unlicensed medicines being related to how readily the NHS would supply the medicine, perceiving that unlicensed medicines are not typically supplied by the NHS or not as easily accessed through the NHS.

*“[An unlicensed medicine is] something that is not... available via the official NHS prescription, via the GP surgery... yeah, an-and it’s issued by a special lab, sort of a private lab and... they are medications which are specifically made up for the individual patient” [INT 2.2].*

One participant described the importance of patients being informed about the licensing status when receiving an unlicensed ‘special’ medicine, as a lack of awareness could have a big impact on supply, for example if they did not appreciate potential delays in ordering.

*“Maybe just letting you know [the medicine is unlicensed] then, and also giving you a heads up that you might not be able to get it from the pharmacy that you go to, or that if you kind of have run out on that day, you can’t just, like say with the aspirin, you can just go up you can buy that over the counter, but you can just go and get it and you know it will be there, whereas with the [unlicensed medicine] spiro, if you were to run out (shakes head)” [INT 2.3].*

#### **5.5.2.1.2 Acceptability of the use of unlicensed medicines**

Participants’ perceptions of acceptability were influenced by factors including the licensing status of the medicine and the perceived risks and benefits. When discussing the licensing status of the medicine the patient described how they were not familiar with the term unlicensed, and this led to questions around the safety of the medicine.

*“I think it’s just that unlicensed label on it that you kind of think, or what is that? Why? Why is that? Why, it kind of makes you wonder if it’s safe” [INT 2.3].*

All participants described their perceived need for the use of an unlicensed ‘special’ medicine, in some cases this was because the licensed alternatives were ineffective or unsuitable for them or their child.

*“[My son] he’s been on patches, ‘cause he had a very severe dribbling, but the patches didn’t work, caused him allergic reaction [sic]” [INT 2.4].*

In other cases, participant perceptions of need were directly related to the positive health outcomes experienced when taking the medicine. All participants described how their medicine had helped to improve their or their child’s health and wellbeing and described how



this had encouraged them to continue taking or supplying the medicine to their child in the future.

*“I, I was... low in energy and much more tired and I feel much better now, so I'm very happy with the... the extra... unlicensed medicines, and I intend to continue with them” [INT 2.2].*

The participant who had not been informed that the medicine their child was taking was unlicensed described how the term ‘unlicensed’ led to them having concerns and potential assumptions of a lack of safety and described the difference in acceptability between off-label and unlicensed medicine with off-label being more reassuring to them and unlicensed medicines being associated with trials.

*“I guess [off-label medicines] that would give you a little bit more like encouragement, if it's been that is, it's not like a totally new medicine we can't know what it does, we know it works in adults, so yeah, that gives you a bit more reassurance that it's not just a trial type thing” [INT 2.3].*

Despite the lack of understanding reported around what unlicensed medicines are, all participants described the benefits to their health experienced while using the unlicensed medicines, which seemed to reduce concerns related to risk and improve acceptability.

*“I feel pretty special 'cause [sic] other things [medicines] didn't help him really, so [the doctors] they've done what they could to help him” [INT 2.4].*

A risk benefit-analysis was evident for one of the participants, who explained their need for the medicine outweighed the potential risks explained to them. The patient explained how taking their unlicensed medicine helped improve their quality of life and well-being so much, that they were willing to accept the known and unknown risks of long-term use as no other treatment had been as effective.

*“It's definitely not a good one [medicine] for pregnancy because it doesn't pass the placenta, but I said, well, I'm not getting pregnant, so can we just forget about that please? And they [hospital doctor] said fine, bone density [is another risk], they'd be paranoid that maybe it would affect how my bones would be long term and I kind of thought well, I just want to live... if I have a bone problem in 10 years' time at least I've lived for 10 years” [INT 2.1].*

Some participants were receiving licensed medicines along with unlicensed medicines, one participant described how the combination of medicines their child had received had saved their life. This further reinforced the perception of need for the medicines and improved

acceptability regardless of the licensing status, as the perceived risks of not receiving treatment had outweighed the risk of receiving an unlicensed medicine.

*“If not the doctors in here, I don't think he [my son] would be with us now...really 'cause they said yeah they said to me he may survive till when he will be 8 years old and now he's 14” [INT 2.4].*

### **5.5.2.2 Theme 2 – Patient perceptions of healthcare professionals impacted by issues experienced**

Participants faced numerous challenges in their journey leading to first being prescribed unlicensed ‘special’ medicines and later on in accessing further supplies. Some participants described complicated processes around first being prescribed an unlicensed medicine with some having to access the medicine privately first, or trying multiple licensed medicines beforehand over the course of years. Once prescriptions had been initiated for the patient, challenges were also experienced across care settings within the NHS. It was reported that GP concerns lead to delays or refusals of further prescribing, disrupting the continuity of supply and for one participant, a lack of consistency in the medicine received in the community. Participants described an ingrained trust towards prescribers, which often helped to reduce any concerns about the unlicensed medicine received, however tensions arising from the process of initial or further prescribing, resulted in poorer relationships with GPs compared to secondary care prescribers and community pharmacy staff.

#### **5.5.2.2.1 Issues faced by patients during their journey from initial prescribing of unlicensed medicines to obtaining regular supplies**

Some participants had difficulties accessing their unlicensed medicine through the NHS and had to buy the product privately when an NHS prescriber would not accept responsibility for prescribing, which resulted in an increased cost for patients.

*“So yeah, as a patient it was a very poor experience because I had to be going here to there [hospital to GP] quite a lot and there was [sic] times where I was just left short... so I paid for privately, so it did get expensive” [INT 2.1].*

One participant also described conducting their own research to find a treatment privately due to a lack of efficacy with the medicines they had already been provided by the NHS.

*“I heard about bioidentical hormones, and it took me a while to do some research 'cause [sic] it's not that easy to find, not that accessible... and I finally arrived at the London clinic, and they were quite expensive and then somehow I got hold of a clinic in Brighton, the Women's hormone clinic and they were more reasonable” [INT 2.2].*

Participants described issues experienced that led to difficulties or delays when accessing their unlicensed 'special' medicines. This included GPs expressing concerns over prescribing of unlicensed medicines leading to them being unwilling to authorise such a prescription, which some participants believed to be due to the unlicensed status of the medicine and the cost of the medicine.

*"I should have been entitled to free [prescriptions], but my GP in Cardiff wouldn't write the script because it wasn't a licensed medication and because she didn't believe the private consultant's recommendation. Even though symptomatically, I was a lot improved, it was all about budgets and they didn't really care." [INT 2.1].*

Participants described how GP non-acceptance of authorising further supplies that were requested by secondary care led to delays while the patient contacted the original prescriber to resolve the situation, and how this situation was experienced more than once showing ongoing issues receiving the medicine in the community.

*"Sometimes when I phone [the GP] to order the medicines, they didn't wanna [sic] give it to me, so then I got to go back to my son's paediatrician [in secondary care] and he had to send a letter that [my son] is on that medicine so they would give him that, so I had few problems with that" [INT 2.4].*

Delays were also reported when the prescriptions had not been sent from the GP surgery through to the community pharmacy in time, delaying the ability of the pharmacy staff to order the medicine and in one case leading to disruption to patient care.

*"My only problem now is that my GP, it's [the unlicensed medicine is] on a repeat prescription as quick as I can get it [sic], but sometimes the GP is late sending it up and then I'm a few days without it" [INT 2.1].*

The ways in which information was transferred between primary and secondary care settings was also highlighted by one participant as an issue that causes delays during transfer of care.

*"The flow of information between paediatrician clinic and GPs, 'cause there is a delay in it, I know the letters should be sent and the letter has been sent, but sometimes they say they has not [sic]" [INT 2.4].*

When accessing the unlicensed 'special' medicine from the community pharmacy, one participant described a variation in the medicine received, with differing brands of the product being supplied, without explanation. This caused some concern to the patient however, the participant reflected that despite the variation in the medicine received, they had experienced no negative outcomes when taking them.

*“A couple of years ago they changed brand like three times in as many months and that was a little bit concerning for me, 'cause I was doing my research and they were saying you know some of them are 76% effective and some of them are 90% and you know, so you could get a variation there, but, like symptoms wise, I didn't feel any worse or any better on any variety, so I was OK with that, but it did make me the cautious at the time” [INT 2.1].*

The same participant had experienced receiving their unlicensed medicine past its expiry date from the community pharmacy, and their treatment was delayed while the pharmacy ordered in a new supply.

*“[The community pharmacy] have dispensed out of date to me and I've come back and said this isn't going to do so...they do try and pull a fast, well I don't think it's the chemist, I think it was the drug company because it's unlicensed, maybe they didn't have demand in that month and they were just trying to shift out their old stock” [INT 2.1].*

#### **5.5.2.2.2 Patient perceptions of how their care, and the responsibility for it, is managed by healthcare professionals**

All participants reported an ingrained sense of trust towards secondary care prescribers and the hospital teams that were involved in initiating the use of the unlicensed medicine, and this trust helped to reassure them of their safety.

*“So for me it didn't matter licensed, unlicensed, and I trust the doctors in here, and I know they wouldn't give him [my son] anything which would cause, you know any harm” [INT 2.4].*

This trust towards healthcare professionals was reported to reduce concerns around the fact the medicine was unlicensed, as it was believed that if the medicine was being supplied by a registered doctor, it would have to be used in line with regulations and therefore would ensure a certain level of safety.

*“Because I am doing it through a recognized physician, I feel that I am very, you know, I'm safe and protected and it's sufficiently regulated in my eyes so that I feel safe, and-and don't have any issues with it.” [INT 2.2].*

However, participants described varying perceptions of trust towards healthcare professionals within different roles, which impacted patient views on who was responsible for their treatment. Participants reported positive feelings towards the prescriber who had initiated their treatment, often viewing them as having the main responsibility for the prescription but also as helping the patient access their medicine.

*“Honestly I credit him [the private doctor] with saving my life really, like even my, I was so tired like my energy levels were really low... he was the first kind of doctor that saw me as a person” [INT 2.1].*

This was reinforced when participants experienced delays across care settings and the original prescribers were seen to write letters to GPs to request the medicine be supplied after the GP had expressed that they were not willing to do so. One participant outlined how when a GP did not feel comfortable prescribing the unlicensed medicine, the hospital staff were able to arrange and supply them with the required medicine to ensure they would not experience a delay.

*“When I couldn’t get medicines from GP, my secretary [sic] of the paediatrician, is my friend’s wife, so phoned her and she quickly organised a script, and I went the same day to the hospital chemist and I had the medicine” [INT 2.4].*

Another participant described how they had experienced issues with GPs feeling uncomfortable authorising supplies of unlicensed medicines, and how subsequent letters from secondary care were sent to primary care to ensure the medicine was supplied on multiple occasions. The participant perceived the secondary care prescriber to hold the responsibility for the prescription as the actual medicine received stated that it was prescribed by the secondary care clinician, despite the GP also having to continue the prescription.

*“The endocrinologist gave me a copy of the letter they wrote to the GP where they were being very stern and they did say this is our responsibility, we are saying prescribe it...I notice as well on the, on the packet, it’s always ‘as prescribed by the endocrinologist’, so it feels like the GP is kind of backing away from responsibility with it” [INT2.1].*

These experiences of secondary care clinicians providing patients with a perceived effective treatment and helping to ensure patients could access the medicine once discharged, resulted in good patient-professional relationships, and helped to foster trust. However, participants did not describe as positive a relationship with GPs often viewing them as a cause for delay or disruption. One patient expressed feeling that the GP did not care about them as a patient and was just taking blood tests during medicine reviews as a requirement without the GP actually knowing if the results were an indication of improving or worsening health. The participant perceived the GP to not understand the clinical situation, or to at least not respond in the same ways compared to other GPs they had encountered. This led to concerns and a lack of confidence in the specific GP that was treating them, that if something was to be wrong, it would not be noticed.

*“So it feels like the GP, liability wise, is just saying ‘as long as I have blood on file it’s OK’ and it doesn’t matter what that blood says, ‘cause [sic], and I suppose that’s a bit concerning, ‘cause [sic] if I was, you know, if I was miss-medicating, or if you know, anything could have happened to me and I don’t think the GP would pick it up at all, it’s like they don’t care which is odd” [INT 2.1].*

Participants all described how the community pharmacy staff were helpful to them when acquiring their unlicensed ‘special’ medicines with pharmacists helping patients manage the lead times needed, and even delivering the medicines when the patient could not get to the community pharmacy.

*“I know them for at least 10 years at least, and I have a few friends in that chemist, sometimes my friends will bring the medicines to me if I cannot get out” [INT 2.4].*

### **5.5.2.3 Theme 3 – Strategies adopted by patients to ensure timely access and continuity of supply when receiving unlicensed medicines**

Participants described a number of different strategies used to ensure they could access a continued supply of their unlicensed ‘special’ medicines. This involved engaging in regular communication with healthcare professionals across settings when issues were experienced and when informing the pharmacy in advance of when further supplies were needed.

Patients also described splitting their supplies, ordering extras or saving supplies as a form of back up in case they were to lose their supplies or if delays accessing their medicines were experienced. One participant even described how their career and life choices had been affected by their need to access the unlicensed ‘special’ medicine in a timely manner.

#### **5.5.2.3.1 Adopting different channels of communication with different healthcare professionals**

As patients receiving unlicensed medicines may have complex clinical cases, some participants described communication with a range of healthcare professionals as part of their treatment, which meant multiple healthcare professionals were involved in their care.

*“We’ve been visiting a hospital every, well few times a week to paediatrician, physio [physiotherapist] and speech [speech therapist], loads of therapies” [INT 2.4].*

Two participants described having to ask to be able to receive their treatment in the community rather than from the hospital as the time involved in accessing the medicine from the hospital was time consuming. In one case a patient had to repeatedly take time off work to attend the hospital as they were required to wait for hours until they would receive their medicine.

*“I was back to them [the hospital] every six months for... bloods and just you know ‘how you feeling’ you know grand, can I go now? (laughs) It was really quick, I’ll be queuing for three hours to get in for three minutes and be discharged, but it’s about probably four years ago now, they said OK, fine ‘cause I, I said look I have to take a day off work to come to you, and we’re not changing anything, can we just accept that I’m on this? And they said fine... so they wrote to my GP and he said I’m happy to discharge her from our care, please keep writing the script and if you have a problem with that, refer her back to me” [INT 2.1].*

Participants reported needing to contact other healthcare professionals when issues were experienced, such as contacting secondary care prescribers when their GP had decided not to continue the prescription for an unlicensed medicine. Participants described how this pursuit of communication was necessary where issues were experienced in order to ensure there would be no treatment disruption.

*“[The GP] They said it’s unlicensed medicines they cannot prescribe, I said you know he’s [my son] being prescribed, but he, by his paediatrician, he cannot go without it, so then [you have to] go back to paediatrician, they had to send the letter again [to the GP]” [INT 2.4].*

One participant described having to contact the GP to issue another prescription when they had accidentally dropped their supplies. The participant described how receiving the prescription from the GP typically took a few days, however in this case they managed to reduce this time by discussing the need with the doctor.

*“I spoke to the doctors at the surgery the next day and they put a rush prescription through ‘cause normally with the doctors you have to wait two to three days to get the prescription signed, so they put a rushed prescription through and took it there and I think I’m sure it’s like if you take it before 12 they can get it the next day, so I kind of put, managed, everyone managed to kind of put a rush order through” [INT 2.3].*

Patients had developed the strategy of informing the GP and or the community pharmacy in advance of when further supplies were needed, in order to manage the extended lead times when acquiring unlicensed medicines. The notice patients had to give to the GP or pharmacy varied between a few days to one or two weeks prior to needing the medicine.

*“Yeah, yeah, especially with the spyro [the unlicensed medicine] I always keep an eye on it, and when it’s kind of, you know, like an inch to the bottom, or whatever, I put the prescription in, and that ‘cause I know that they’ll need a couple of days to get*

*it, so yeah, I always watch that one a little bit more, 'cause I know that's the one that will take a while, well not a while but a couple of days to get" [INT 2.3].*

#### **5.5.2.3.2 Managing and storing supplies**

Participants described the background to them formulating individual contingency strategies to ensure that their supplies were never disrupted. All participants were aware they would not be able to access their unlicensed medicine in the same day if needed due to the extended lead times described above. This resulted in concerns around if they were to lose or accidentally destroy their supplies and even concerns about the medicine being stolen.

*"I do worry about if I go on holiday that I have to bring enough supply [of the unlicensed medicine] and you know I split my supplies in case I get robbed or whatever" [INT 2.1].*

Many participants had experienced some issue with supplies, one participant shared how they had accidentally dropped their medicine bottle and as they knew they would have to wait a few days to access more, described syringing the medicine off the floor. As a result of these concerns and experiences some participants described splitting, saving or ordering extra supplies in order to have a back-up supply at home, in case anything were to happen to their main supply or if they were to experience delays.

*"I smashed the bottle accidentally and it was, I didn't have a back up 'cause they don't [pharmacy staff], they only give you the one, so I had to syringe it off the floor, because I didn't have any any [sic] backup, so now I pour a bit into a spare bottle just in case, 'cause I know I can't easily get it" [INT 2.3].*

Another participant described buying supplies of the medicine privately and using it when delays accessing their medicine from the pharmacy had occurred, rather than going without any medication.

*"What I've done is I've bought a couple of months' [supply of the unlicensed medicine] privately on the quiet just so I'm not short because quite often I go to collect it and it's not ready, they're [the pharmacy are] only ordering it then, or they're only reminding the GP then, and there's a lag so it wouldn't be unusual for like for a month prescription I actually have to make it last five or five and a half weeks." [INT 2.1].*

One participant described altering the doses to smaller amounts compared to what is originally prescribed, in order to manage the lead time and ensure their child would not experience a day without treatment.



*“So I know we won't run out even if there is one of 24 hrs delay, yes and I can, I can adjust, his medicines too so I can give him 5 mls per day, not 7 1/2 yeah, yeah, especially when it's weekend when he doesn't need to go to school” [INT 2.4].*

#### **5.5.2.3.3 Limitations imposed by the use of unlicensed medicines on patients' personal and professional life**

One participant described how their life decisions were impacted by their need to manage their supply, for example they could not go to visit family during the Covid-19 lockdown for more than three months as they were not allowed to transfer their prescription to a different location and could not be prescribed the medicine for longer terms.

*“They said three months is at our discretion, this is the GP now, the three months is at our discretion for a holiday and we don't care, you should be in your residential address, so that's been sad because I want to be able to be with my family more” [INT 2.1].*

The participant also described how they would not be able to move locations or apply for jobs outside of Wales as they did not feel confident their supply would be continued, and perceived this to be a limitation that had been imposed on their professional life as a direct result of needing an unlicensed medicine.

*“It is quite distressing I suppose, 'cause like if I was to consider for work, there is opportunities for me to work abroad and I actually have to think about how would I get my drugs... because you can't post them so it has held me back career wise” [INT 2.1].*

## **5.6 Discussion**

The study aimed to explore the views and experiences of patients, or the parents and carers of those, who receive unlicensed 'special' medicines. To the researcher's knowledge, the results provide the first insight into the views and experiences of patients, parents and carers around the use of unlicensed medicines specifically in Wales.

### **5.6.1 Patient awareness of licensing status and acceptability of receiving an unlicensed medicine**

The results highlight inconsistencies in the ways patients were informed they were receiving an unlicensed medicine, with some being supplied physical information, others verbal information and in one case, the patient was not informed at all. Recent evidence from within England has also identified patients from within primary care who were not informed they

were receiving an unlicensed medicine, despite their medicine originally being initiated in secondary care (Donovan *et al.*, 2021). Although the authors did not identify large numbers of participants who were not informed, the results reinforce findings of study 2, in that the methods and approaches used to inform patients vary across the UK, resulting in some patients not being informed that they are being prescribed an unlicensed medicine. This could be a direct result of the inconsistent guidance provided to healthcare professionals on the topic. In particular, some guidance is suggesting patients should always be informed the medicine is unlicensed (ABPI 2019)(BNF 2021b), while other organisations or professional bodies state that in cases where the licence status may cause concern for patients, drawing attention to it may not be necessary (GMC 2021)(AWMSG 2021). Although the latter guidance aims to alleviate patient concerns, this has implications on informed consent and patient-centred care.

Patient-centred care aims to involve the patient in decision making around their treatment and takes into account the patient's views and needs (NWSSP 2021). Patients have legal and ethical rights to make decisions around their own treatment and in order to provide valid consent, patients must be competent to make decisions about their care and have been provided with enough information to effectively make an informed decision. In cases where the patient has not been given suitable information, their consent would not be legally valid (Welsh Government 2017b). Patients cannot be at the centre of care if they are not aware their medicine is unlicensed as they would not have been able to have discussions around this, and therefore cannot make a fully informed decision to receive it. The information provided in the guidance documents and the findings gained from study 2 highlight a need for a clear, consistent information to be created for healthcare professionals to support conversations around the use of unlicensed medicines and ensure that patients are informed in a consistent manner.

Another aspect of empowering patients to be involved in their own care is the use of clear information. The findings from study 2 highlight that not all patients were supplied with information about the use of unlicensed medicines and suggest a need for the development of a clear, consistent patient information leaflet. The use of patient information leaflets has been reviewed many times within the literature. The benefit of providing patients with information leaflets about their medicine has been recognised by the MHRA (2020c) who suggest that good information can aid patients in being involved in decision-making. Many different organisations have created information leaflets that can be supplied to patients receiving unlicensed medicines (NHS 2016, Gloucester hospitals NHS 2018, BCPFT NHS 2019, Medicines for children 2020), however it is unclear how frequently these information leaflets are used within practice. Additionally, the content and detail of information presented

in these documents varied, with some providing information about the different types of unlicensed medicines and others simply describing the difference between licensed and unlicensed. Differences were also noted with some offering guidance about the short expiry dates associated with unlicensed medicines and providing advice on how to ensure consistent supplies are accessed, while others did not mention the need to order the medicine, potentially adding an extra level of confusion to patients who may be attempting to use these resources.

In order to create good quality patient information leaflets Lampert *et al* (2016), suggests that 4 steps must be met, this includes considering the needs of the target population, assessing the readability of the information, reviewing the suitability of the leaflet and gaining patient feedback and involvement. The involvement and co-creation of patient information leaflets with patients has also been suggested by Herber *et al* (2014), who found that the content and the language used within patient information leaflets has been seen to impact patient perceptions, with information provided around risk leading to increased patient concerns and in some cases, the concerns lead to non-adherence. The co-design of patient information leaflets may help to improve their content and may be important when informing patients about the use of unlicensed medicines as concerns caused by the terminology have been reported by a participant in study 2 and by patients within the existing literature (Aston *et al.*, 2019; Donovan *et al.*, 2021). The participant who had not been informed their child was receiving an unlicensed medicine described how the term unlicensed had led to concerns around the safety of the medicine, with off-label medicines offering more reassurance in comparison. Aston *et al* (2019), conducted semi-structured interviews with parents and the results highlighted one participant whose medicine had a large label stating the medicine was unlicensed and described how this had caused concerns for the family members. Although the study was not focused on the use of unlicensed medicines, it supports the finding that the terminology itself can cause concerns for patients. More recently, Donovan *et al* (2021) also identified a patient who described how the unlicensed status led to questioning the safety of the medicine and if the medicine had been sufficiently tested, or was being tested currently. Although in both studies only one participant was identified who described concerns around the associated terminology for unlicensed medicines, the findings suggest that the terminology used may impact patients' perceptions of acceptability and further supports the need to inform and educate patients receiving unlicensed medicines in order to increase understanding and reduce concerns.

Despite the concerns raised above, all participants' acceptability of receiving an unlicensed medicine was increased due to their perception of need. The necessity-concerns framework outlines that patient adherence behaviours are directly impacted by a cost-benefit analysis

specifically involving concerns about the risks of taking the medicine and their own perceptions of need (Horne *et al.*, 1999; Horne *et al.*, 2013). This was evident with multiple participants in study 2 with one patient actively saying they were willing to accept the known and unknown risks of receiving their unlicensed medicine due to their perception that this was the only medicine that had been effective for them and had improved their health and well-being. The differences in patients' perceptions of need and concerns has also been seen to differ among other patient groups. Horne *et al* (1999), explored the perceptions of four different patient groups and found that asthmatic and cardiac patients were significantly more likely to view the benefit of the medicine as being outweighed by the cost of the medicine compared to oncology and dialysis patients. As patients receiving unlicensed medicines may have complex clinical conditions, it is understandable that their perceptions of need may be increased. Hence, the concerns raised about the terminology, as discussed above, may be reduced if the justification for the need of an unlicensed medicine is clearly explained.

### **5.6.2 Impact of issues and challenges faced when trying to access unlicensed medicines**

Patient perceptions of need and associated acceptance of the potential risks of using unlicensed medicines were so strong that concerns around not being able to access the medicines were reported more frequently than concerns about the medicine being unlicensed. Participants reported a range of experiences that led to delays or disruption of treatment when accessing their unlicensed medicine, including difficulties accessing the medicine through the NHS, GPs not feeling comfortable enough to continue the prescription, and inconsistent medicines received from the community pharmacy.

This is in line with existing literature that supports difficulties for patients accessing unlicensed medicines after discharge. Wong *et al* (2006) found that a third of participants had experienced issues that caused delays and disruption to receiving their unlicensed medicines, including GPs not wanting to prescribe and community pharmacy teams being unable to acquire the medicine needed. Although the study was conducted 15 years ago, and explored the experiences related to paediatric patients, it involved a large number of participants, and the findings highlight that the issues faced by patients when trying to access their unlicensed medicine in the community after discharge have remained consistent overtime and are ongoing across the UK.

The transfer of care is recognised by the World Health Organisation (WHO) as a time where patient safety is at risk due to the involvement of multiple healthcare professionals across care settings and the potential for clinical information to be lost (WHO 2007, WHO 2016).

Despite the limited evidence around the use of unlicensed medicines, multiple studies have highlighted issues during transfer of care, with a recent systematic review highlighting that medication errors and adverse drug events were common after discharge from hospital, with the median rate of medication errors after discharge from hospital for adults being almost 50% and 20% of adult patients being impacted by adverse events (Alqenae *et al.*, 2020). The systematic review included evidence from many countries including the UK, gained over 29 years, strengthening the findings and further highlighting the risks associated with transferring between hospital and the community. WHO (2019) have outlined many suggestions to improve medication safety during transfer of care, such as increasing communication and cooperation across all care settings. Methods suggested to improve this included the use of electronic health records that could contain information about a patient's medical use across all care settings, and ensuring that healthcare professionals and patients are provided with detailed medicine lists.

Shared care agreements support the transfer of care and involve detailed information provided by the recommending consultant to be supplied to the GP requested to continue the prescription. The GMC (2021) suggest that when shared care agreements are made, GPs should be provided with information about the medicine such as the dose and method of administration and have a protocol agreed for treatment. Shared care agreements with treatment protocols have been found to increase prescribers' confidence when requested to continue prescriptions for unlicensed medicines (Crowe *et al.*, 2009). This suggests increased communication and agreements between primary and secondary care staff, prior to the patient being discharged could reduce the delays and challenges reported by patients, when individual prescribers are not willing to continue the prescription. The Welsh Government's plan for 'A Healthier Wales' highlights the importance of a seamless system in which multiple services will be centred around the patient, providing support throughout the entire patient journey (Welsh Government 2021b). For unlicensed medicines, this could involve healthcare professionals working together to put prescribing agreements in place across care settings and could even advise community pharmacies about suppliers to ensure the medicine received is consistent after discharge. A seamless system such as this could help to reduce the delays with accessing a prescription for an unlicensed medicine in the community after discharge and could provide reassurance to patients that they will be supported when accessing their medicines.

Patients described how the issues and delays experienced led to concerns around the accessibility of their medicine if they were to lose or accidentally destroy their supply, and this resulted in the development of specific strategies to ensure continuity could be maintained. Husain, Davies and Tomlin (2017), reported similar findings after conducting

interviews with the parents and carers of children who receive unlicensed medicines. The parents and carers described experiencing delays such as GPs not willing to continue prescriptions, and delays when accessing the medicine from the pharmacy. The parents and carers explained how the issues faced led to a need to take the initiative and manage and organise the ordering process themselves. Other strategies described, such as storing supplies at home, posed their own challenges due to the short expiry dates, which resulted in concerns around accessing replacement supplies if medicines were to be lost or spilled. Although the study only involved 15 participants, the findings further support the issues faced by patients when trying to access unlicensed medicines and shows that patients across the UK are required to take on increased responsibilities in order to manage supplies. The findings suggest not only that patient awareness is vital in ensuring the patient can take on the increased responsibilities, but a need for patient reassurance around the accessibility of their medicine.

The challenges reported by participants in study 2 and the impact of short expiry dates could result in an increased risk to patient safety, with one participant describing syringing the medicine off the floor as they knew they would not be able to access replacement supplies the same day, and another receiving medicines past their expiry date from the community pharmacy. Safeguarding patient safety and wellbeing is emphasised in both the duties of doctors in the GMC's good medical practice guidance (2019) and the GPhC's standards for pharmacy professionals (2017). However, as a result of the lack of accessibility of unlicensed medicines and the short expiry dates, patients were left to develop their own strategies to manage supplies which could potentially lead to unsafe uses. Patient safety is at risk when a medicine is past its expiry date, as the medicines may not be as safe to take or as effective (NHS 2020). This may be especially true for unlicensed medicines, where the expiration date provided should "*include a margin of safety*" based on results of stability testing (MHRA 2021, pp.24). A systematic review found that although many medicines remain stable after their expiry date and could have their expiry extended, this is dependent on the individual medicine itself, with some forms appearing to be more stable than others when approaching their expiry (Zilker, Sörgel and Holzgrabe 2019). This supports the need for healthcare professionals to be aware of the risks associated with taking specific unlicensed medicines after they have expired, so that they can provide individual guidance to patients around if it would be safer to take the medicine, or miss a dose.

Community pharmacists have a responsibility to ensure the quality of medicines they supply by checking the excipients and the expiry dates (NHS 2019b). The situation described by participant 2.1 in 5.5.2.2.1 where they received their unlicensed medicine past its expiry, could have been due to the pharmacist not checking the expiry date, or could be the result of

the short expiry date if the patient was late in collecting the medicine. However, in either scenario patient safety was at risk and delays were experienced while further supplies were accessed.

Many medicines have short expiry dates, and this has been highlighted across many countries including the UK for medicines used in the treatment of cancer, with many medicines only having a 24hr expiry (Gilbar *et al.*, 2017). Short expiry dates have also been highlighted as an issue when gluten free products are prescribed and supplied in community pharmacies, which can lead to waste if patients do not collect their products when they have been obtained by the pharmacy (Department of Health and Social Care, 2018). When looking at community pharmacy dispensing errors in England, Franklin and O'Grady (2007) identified multiple medicines being supplied after they had expired, and in one case the medicine was dispensed three months past its expiry date. The findings from study 2 and from within the literature further support the importance of all healthcare professionals conducting checks to ensure the medicines supplied are safe, and highlight the issues faced when accessing medicines with short expiry dates in the community.

This experience of receiving their unlicensed medicine past its expiry date also impacted the patient's perception of the suppliers. The patient believed the suppliers had provided the medicine knowing it was expired or close to its expiry date, and questioned whether the suppliers may have been wanting to get rid of stock rather than manufacturing new products. To the researcher's knowledge the patient's perception that suppliers may be more focused on selling and using old stock, which is nearing its expiry, rather than manufacturing newer supplies has not been reported previously within the literature and offers a unique finding when exploring patients' views on the healthcare professionals involved in the different stages of care when receiving unlicensed medicines.

Participants described how the issues and delays experienced when accessing their unlicensed medicines had impacted their perceptions of the healthcare professionals involved and how they viewed responsibility for their care to be managed. The participants who had first received their prescription from a private doctor reported very positive relationships, perceiving that the private doctor viewed them as a person rather than set of symptoms and that NHS staff were restricted and only able to prescribe certain medicines. In the cases where the specific medicines were not effective, patients felt the only option was to seek private treatment. As NICE and the AWMSG are responsible for deciding which medicines are available on the NHS (see chapter 1.2.1), when they do not recommend the use of certain unlicensed medicines, patients may still be able to access a prescription for the medicine from a private doctor (NICE 2021b). However, this could also have implications

for patient safety if the recommended medicines provided by the NHS were not effective and patient treatment would rely on maintaining a financial status to be able to pay for the medicine privately. Hancock *et al* (1999) found that in England, 63% of the 1,506 members of the general public involved in a survey and interview study, felt they could access private dental care faster in case of emergencies compared to the NHS, and some participants expressed how they would want to have private treatment if they had enough money to meet the costs. Although the study was focused on dentistry, it highlights similarities in patient perceptions that private care provides faster treatment when faced with emergencies with a participant in study 2, who explained how they had accessed their medicine privately when they were faced with delays in accessing the medicine through the NHS. The findings suggest that patients may perceive the NHS to not be as reliable as private care in case of emergencies and despite an overall appreciation for the NHS, it was viewed to have limitations.

When medicines had been received by participants from within the NHS, good relationships with secondary care prescribers and community pharmacy teams were reported. However, when GPs were unwilling to continue prescriptions for unlicensed medicines, this was seen as an unnecessary delay in the eyes of the participants who did not understand why, if the medicine was recommended by a specialist and the community pharmacy team were happy to supply, the GP would not be accepting of this. The perception that GPs were not as responsible for the prescription of unlicensed medicines was also reported by patients in another study (Husain, Davies and Tomlin 2017), where patients described GPs' role as simply responsible for signing the prescription. Multiple other studies have highlighted the public perception that the GP is simply "*a middle man*" and were viewed as not as knowledgeable compared to specialists, or that better care would be received in hospitals (Biddle *et al.*, 2006 pg.928; MacKichan *et al.*, 2017pg.9-10). The results showcase a lack of patient understanding related to GP responsibilities, which negatively impacted the patient-GP relationship and suggest a need for information to be provided to patients about the roles and responsibilities of the different healthcare professionals involved in their care.

However, it may not only be patients who are unaware of the specific roles and responsibilities of individual healthcare professionals, with tensions between primary and secondary care prescribers being reported within the literature. Secondary care prescribers and GPs have reported feeling that their counterparts were '*dumping*' work on them, with secondary care prescribers feeling as though GPs showed more resistance in shared care and both groups having conflicting views on the others responsibility (Samson *et al.*, 2016). Tensions were also reported by Buture *et al* (2020) with one secondary care prescriber describing disagreements they had experienced with GPs not wanting to supply specific



unlicensed medicines (verapamil and lithium) and perceived that if NICE were recommending it, the GP should supply it. The findings suggest that secondary care prescribers may also not be aware of the specific role and responsibilities of GPs and further highlights the need for clear information to be created and provided to healthcare professionals across settings and patients to improve relationships with GPs and ensure a seamless transfer.

It is important to note that GPs are responsible and take on liability when they continue or initiate prescriptions for all medicines. The General Medical Council advises that when GPs prescribe unlicensed medicines, they must feel satisfied with the available evidence for the use of the medicine, take responsibility for the prescription and record the reasons why the unlicensed medicine is being prescribed (GMC 2021). Therefore, when a GP turns down a request to continue a prescription, although potentially disruptive to patient care, this can be justified and may be good practice in the best interest of the patient if the prescriber has concerns for patient safety. This could include cases when a GP does not feel the medicine is the most suitable treatment or are not familiar with why and how the medicine should be used. To improve the relationship between patients and GPs, and subsequently improve timely access to unlicensed medicines when appropriate, information could be provided to patients and secondary care prescribers that explains GPs' responsibilities and the legal implications when prescribing medicines, as well as the GPs' right to decide not to prescribe. The BMA (2004) have created guidance that explains GPs' rights and responsibilities when prescribing medicines in general and provides explanations as to why one GP may be willing to prescribe a specific medicine, but another may not, or why a GP may not be willing to prescribe even after an unlicensed medicine has been recommended by a consultant. Although this guidance is not aimed at patients and is not focused on the use of unlicensed medicines, it provides a good example of how information around GP roles can be provided in a clear understandable way. Clear guidance could potentially reduce the perception that GPs are less caring by helping the patient to better understand the roles of the healthcare professionals responsible for their care and by clarifying liability of GPs to secondary care prescribers, potentially alleviating tensions.

Overall, participants reported multiple delays experienced when trying to access unlicensed medicines across the patient journey. Difficulties were faced when trying to access an unlicensed medicine through the NHS, when the differing perceptions of acceptability among healthcare professionals led to disruptions between care settings, when extended lead times had to be managed, and when inconsistent medicines were received over time in terms of formulation, or brand. The creation and use of a consistent information leaflet for patients receiving unlicensed medicines, and increased communication between primary and

secondary care teams prior to the patient being discharged could help to increase awareness and the patients' ability to manage lead times effectively, reduce concerns and improve patient-centred care. Giving patients and prescribers an understanding of the responsibilities associated with prescribing unlicensed medicines in different care settings could help to improve the relationship between the GP and patients or hospital prescribers and increase understanding as to why GPs may not always be willing to continue prescriptions when requested.

### **5.6.3 Limitations**

The researcher acknowledges several limitations that were faced during the research process. As the recruitment period was impacted by the Covid-19 pandemic, this limited the amount of time the researcher had to access participants, and as gatekeepers and online advertising were utilised to ensure the researcher did not need access to patient data, the full number of potential participants invited cannot be determined, making it hard to estimate the response rate. Despite the delay in the start of recruitment, increased efforts were made by the researcher to increase response rates, using multiple methods such as offering monetary incentives for any participant who completed an interview and following up with the gatekeepers to send out reminders and follow-ups.

The researcher also recognizes the small and non-representative sample gained, and this could be partly a result of the restrictions enforced during the Covid-19 pandemic and the increased stress reducing capacity for some community pharmacy sites. The results may not be generalisable for all patients receiving unlicensed medicines in the UK, and there is a limited amount of literature exploring patient views in the UK for comparison. However, as the findings from this study are consistent with and supported by the previous literature available, it suggests the results are valuable and help to add to the existing knowledge around the use of unlicensed 'special' medicines in the UK.

### **5.6.4 Reflections**

The interviews conducted provided an understanding into the strategies adopted by patients when accessing their medicine and the impact that receiving unlicensed medicines has had on their health and quality of life. The researcher had originally planned to have a much larger sample in order to produce more transferable results however, the information gained in this study is valuable and adds to the existing knowledge within the literature. The results support previous findings that patients are required to adopt multiple strategies to ensure continuity when accessing their medicines and have concerns about the timelines involved in needing to order their medicines.

When considering the recruitment strategy used, the researcher valued the involvement of gatekeepers. Gatekeepers identified within community pharmacies were essential in making sure participants would be invited into the study. However, when trying to identify gatekeepers in secondary care more challenges were faced, some of the contacts made suggested they were too busy to act as a gatekeeper, which was understandable as healthcare professionals were facing an unprecedented workload during the Covid-19 pandemic. The experience highlighted the value of having gatekeepers identified before the start of recruitment to reduce delays identifying and arranging agreements during the recruitment period.

Patients who need unlicensed medicines face a unique set of challenges which requires increased involvement in order to manage their supplies. Although this has been seen to be effectively managed by patients and healthcare professionals working together, it results in concerns that patients receiving licensed medicines do not need to consider. The researcher perceived that the best way to improve the overall patient experience would be to increase awareness so that the challenges could be managed effectively and to address and reduce the concerns caused through the knowledge that the medicine could not be accessed within the same day if needed.

### **5.6.5 Conclusions**

To the researcher's knowledge, the findings of this study provide the first insight into the views and experiences of patients who receive unlicensed 'special' medicines specifically in Wales. A unique finding was that one patient had described altering the doses for their child themselves to ensure they had enough supply, a practice that could potentially compromise patient safety. Overall, the results build on the existing body of literature and further support the challenges and delays faced by patients when accessing unlicensed medicines in the UK. The results highlight that not all patients were informed when they were prescribed an unlicensed medicine and suggests this may cause delays or disruption to patients if they are not aware of the extended lead times and the need to order the medicine in advance. To reduce the chance of delays, it is important that patients are at the centre of care and provided with enough information to effectively take on the increased responsibilities required. The co-creation with stakeholders and patients of a consistent patient information leaflet to provide information around the unlicensed status, the implications this has on the accessibility, primary and secondary care prescriber rights and responsibilities and emergency supply processes if supplies were lost or destroyed, could all contribute to increasing patient involvement, reducing delays, improving the patient-GP relationship, and

reducing patient concerns around the accessibility of their medicine. This ultimately aligns with the Welsh Government's strategy for 'A Healthier Wales' (Welsh Government 2021b).

## **6. Study 3 – Semi-structured interviews with prescribers in primary and secondary care**

### **6.1 Overview of chapter**

The previous study chapters explored how unlicensed medicines are acquired, supplied, accessed and received from the perspectives of community pharmacy staff and patients. Study 3 focusses on how therapy with an unlicensed medicine is initiated or maintained from the perspective of prescribers. The chapter consists of a brief introduction to the study, providing some background information about what is currently known on the research topic and the justification for the research. The specific aims and objectives of the study will be clearly outlined. Following this, a detailed description of the methods used to explore the views and experiences of prescribers in primary and secondary care who prescribe unlicensed ‘special’ medicines will be provided. The sampling and recruitment strategies employed will be outlined in detail, including the eligibility criteria used and the role gatekeepers played in recruitment. Following this, the materials and technologies used to conduct the research and a description of the data processing and analysis techniques used will be provided.

This will be followed by a detailed examination of the results of the study, where the participant characteristics will be described along with an in-depth description of each theme and sub-theme constructed. This will include the provision of quotes taken directly from the interview transcripts that will be used as evidence.

Lastly, a discussion on the findings will be provided, which will include examining the results in the wider context of the existing literature. The limitations of the study will also be addressed along with some reflective notes about the research process and final conclusions.

### **6.2 Introduction**

Prescribers have the important role of determining when the use of unlicensed ‘special’ medicines is necessary and deciding whether to initiate a therapy via prescribing such medicines, or continue prescriptions for products initiated previously by another prescriber. In line with the MHRA guidance (MHRA, 2014a), prescribers should only prescribe an unlicensed medicine if there are no licensed alternatives available to meet the clinical needs of the patient.

The introduction and systematic review chapters (see chapter 1 and 2) highlight how the guidance available to healthcare professionals can be confusing and can contain inconsistent information about what unlicensed medicines are (Donovan *et al.*, 2018), which will inevitably impact on prescribers' attitudes towards initiating or maintaining therapy with an unlicensed medicine. The chapters also highlight how prescribers' views and perceptions of acceptability can directly impact prescribing behaviour and patient care. The awareness around and confidence of what unlicensed medicines are, and when they are used in general, appears to be lacking across prescribers (Donovan *et al.*, 2016). However, the confidence prescribers feel has been reported to differ across care settings, with secondary care prescribers reporting higher levels of confidence when prescribing unlicensed medicines than those in primary care (Chisholm, 2012). Specific concerns held by prescribers have been highlighted, such as concerns around the safety of the use of unlicensed medicines and their own legal responsibilities (Wong *et al.*, 2006; Mukattash *et al.*, 2011). The limited literature available suggests that the decision to prescribe unlicensed medicines is impacted by multiple factors such as the individual medicine required, the information received across care settings, prescribers' own knowledge and experiences and the cost of the medicine (Crowe, Tully and Cantrill, 2009). Despite evidence from within the UK, to the researchers' knowledge, there are no studies exploring the views and experiences of prescribers specifically in Wales where the responsibility for NHS Wales lies within the Welsh Cabinet Secretary for Health and Social Service after devolution. As a result of the devolution, there are differences in how prescriptions are managed, for example, Wales removed prescription charges for patients in 2007 (Carlisle, 2017). Since prescription charges have been abolished in Wales an increase in the number of prescriptions has been reported (Groves *et al.*, 2010; Alam *et al.*, 2018). Therefore, prescribers may view the use of unlicensed medicines differently to those in England who would have to consider whether patients could afford to access the medicine as unlicensed medicines can be much more expensive than licensed medicines (Griffith 2019). In order to address the overall aims of the thesis and explore whether we can provide recommendations to improve the patients' experience, we must have an understanding of the views and experiences of those involved throughout the different stages of the patient journey or supply chain through the healthcare system. By gaining an insight into the perceptions of prescribers within Wales, evidence can be used to generate recommendations and either support findings previously gained from other areas of the UK or highlight findings specific to Wales.

### **6.2.1 Study 3 aims and objectives**

The aim of study 3 was to explore the views and experiences of prescribers in primary and secondary care who have experience of initiating or maintaining therapy with unlicensed 'special' medicines.

#### **Objectives:**

- To investigate prescribers' understanding of unlicensed 'special' medicines and their use in practice;
- To explore prescribers' perceptions of safety and quality of unlicensed 'special' medicines from different sources;
- To investigate prescribers' experiences around prescribing unlicensed 'special' medicines, manufacturing timelines and delay obtaining treatment;
- To explore prescribers' approach towards initiating or maintaining therapy with an unlicensed 'special' medicine.

### **6.3 Ethical approval process**

The project was funded by the Knowledge Economy Skills Scholarships (KESS 2), with contributions from an unlicensed 'special' medicines manufacturing unit based in South Wales. As the study involved participation from healthcare professionals working within the NHS, NHS ethical review and approval was required. The application for ethical review was completed alongside the application for the ethical approval of study 2 and this process is described in the previous chapter (see chapter 5.3).

### **6.4 Methods**

As a result of the large number of unlicensed medicines available for a range of clinical uses, it was anticipated that prescribers may have differing views and experiences, especially in cases where unlicensed 'special' medicines are made specifically to treat the clinical needs of individual patients. Differing experiences were also anticipated across primary and secondary care settings, with GPs who may be required to prescribe a variety of unlicensed medicines for a range of conditions in a more varied patient population, having different experiences compared to prescribers within secondary care who may prescribe unlicensed medicines associated with a particular population group or speciality. As described in the previous chapters, in order to explore and better understand each participant's individual experience, a constructivist research paradigm with a qualitative phenomenological

approach was selected (see chapter 3.2 and 3.3), which involved the use of semi-structured interviews (see chapter 4.4). In this way the individual participant's subjective reality could be explored and obtained, while allowing them to raise issues of importance to them.

### **6.4.1 Data collection materials and technologies**

Prescribers in primary and secondary care both play an important part in prescribing unlicensed 'special' medicines. Secondary care prescribers can initiate treatment and discharge the patient back into the community, whilst primary care prescribers can also initiate treatment and are additionally required to take on responsibility for and continue prescriptions for patients who have been discharged and transferred from secondary care (NHS England, 2018). The researcher, after discussions with the steering group (see chapter 3.6), created two separate interview schedules for prescribers, one aimed at exploring the views and experiences of prescribers working within primary care and one aimed at exploring the views and experiences of prescribers working within secondary care (see Appendix 6). The questions were aimed to get participants to outline and describe the process that takes place when prescribing initial therapy or continuing prescriptions for the use of unlicensed 'special' medicines, along with gaining an insight into their views and perceptions around their role, the use of the medicines and their associated experiences.

#### **6.4.1.1 Study documentation development**

Development of the interview schedule was an iterative process based on literature review, the study aims, and feedback provided by the SSG (a teleconference was also arranged with the assistant head for the NHS specialist pharmacy service to gain feedback on the interview schedules). Any recommendations for change were discussed and incorporated into the final version. Examples of some changes made to the interview schedules using the SSG feedback was the inclusion of a question exploring how maintenance therapy with unlicensed 'special' medicines is reviewed short-term and long-term, and the creation of two separate schedules so questions could be tailored to individuals' roles. The researcher had originally created one interview schedule that included more general questions, with options for selecting additional questions related specifically to either primary or secondary care, such as a question about monitoring patients. After gaining feedback from the SSG it was thought that this would be confusing, and the original schedule was used to create two schedules so that questions could be specifically aimed at gaining the perspectives from within the different care settings. The question about monitoring patients was changed to ask about reviewing the use of unlicensed 'special' medicines over time, as it was perceived that in a clinical setting, monitoring patients would be a part of how unlicensed 'special' medicines are reviewed. The interview schedule for primary care clinicians focussed on the



processes involved in prescribing unlicensed medicines for the first time or continuing prescriptions for unlicensed medicines initiated previously. The interview schedule for secondary care clinicians focussed on the process of prescribing unlicensed medicines for the first time and transferring care when a patient continues to need an unlicensed ‘special’ medicine across care settings. Study documentation in addition to the interview schedules included a cover letter for gatekeepers in primary care, a cover letter for gatekeepers in secondary care, an invitation to participate, an information sheet, and a consent form (see Appendix 6). No recommendations for change were made by the SSG on any of these documents. Technologies used to record and store the data are as described in study 2 (see chapter 5.4.1).

## 6.4.2 Sampling and recruitment strategy

The sampling frame included prescribing clinicians working in primary and secondary care in Wales, who have experience in prescribing unlicensed ‘special’ medicines. Potential participants were identified using a mix of stratified, purposive and convenience sampling and participants were required to have at least 1-year experience working as a prescriber, to increase the likelihood that they would have had some experiences prescribing unlicensed ‘special’ medicines. The inclusion and exclusion criteria can be seen in table 6.1. Participants who met the inclusion criteria became the sample population. All participants involved in study 3 were presumed to be aged 18+ due their profession and registration to the General Medical Council (GMC), the regulatory body of doctors within the UK.

**Table 6.1** Inclusion and exclusion criteria for participants in study 3

Eligibility criteria	Prescribers within primary and secondary care
<b>Inclusion Criteria</b>	
Population	<ul style="list-style-type: none"> <li>Individuals who work in primary or secondary care with the role of prescribing medicines.</li> </ul>
Experience	<ul style="list-style-type: none"> <li>A minimum of 1 years’ experience prescribing medicines;</li> <li>Experience prescribing unlicensed ‘special’ medicines.</li> </ul>
Communication	<ul style="list-style-type: none"> <li>Ability to provide informed consent assumed due to the professional registration required of prescribers in the UK (i.e. the GMC).</li> </ul>
<b>Exclusion Criteria</b>	
Experience	<ul style="list-style-type: none"> <li>Individuals with less than 1 years’ experience prescribing medicines;</li> <li>Individuals who have no experience prescribing unlicensed ‘special’ medicines.</li> </ul>

As the study involved recruiting prescribers from within primary and secondary care, the methods used to recruit participants from these settings differed and are outlined below.

#### **6.4.2.1 Recruiting prescribers from within primary care**

Participants in primary care were recruited using a mix of purposive and convenience sampling. Prior to the start of recruitment, the researcher had identified a member of the Primary Care Research Incentive Scheme (PiCRIS) who agreed to act as a gatekeeper and disseminate the study information to all potential GP participants who were part of this scheme across Wales. However, during the course of ethical approval process, PiCRIS was dismantled, and this route of recruitment was no longer available. The original gatekeeper agreed to disseminate the study information for the sites that were previously part of PiCRIS in that individual's health board. In order to broaden recruitment and gain access to the remaining surgeries, as originally intended, the researcher engaged with the individual health board facilitators. In response, some of the facilitators provided a list of current research active sites that were originally part of PiCRIS. Not all health boards chose to supply the researcher with the list of sites to be contacted; instead, some agreed to act as a gatekeeper themselves and disseminate the study information directly to those sites. Where details of sites were provided, the researcher contacted the surgeries directly and supplied the study information to the practice manager, to act as the gatekeeper and disseminate the information to GPs.

The researcher asked gatekeepers of individual surgeries and health boards to resend the study information as reminders to all potential participants one month after initial emails were sent. If any potential participants were interested, they were instructed to contact a member of the research team directly, and if any had not contacted the researcher after the reminder was sent, it was presumed that they did not want to participate and no further contact to recruit them was made. In an attempt to increase the sample size gained the researcher decided to widen recruitment to GPs with a dual role in academia, either contracted by the University as research fellows or as academic fellows.

#### **6.4.2.2 Recruiting prescribers from within secondary care**

A mix of stratified, purposive, convenience and snowball sampling were used to identify and recruit potential participants from within secondary care. Following the guidance of the SSG, the researcher chose to focus recruitment within specific clinical areas. In this way, stratified sampling was used to include prescribers working within gastroenterology, paediatrics and dermatology departments as these areas were perceived to use high numbers of unlicensed 'special' medicines.

Recruitment took place in a number of ways, involving the researcher contacting the health board facilitators and asking for contacts within the specified departments to be identified.

Health board facilitators were asked to provide contacts within gastroenterology, dermatology and paediatric departments who could act as gatekeepers for the study. Different health boards had different approaches to this: some health board facilitators agreed to act as gatekeepers themselves and disseminated the information to individuals within the required departments, while others provided contacts for the researcher to reach out to directly. Where the health board facilitator agreed to act as a gatekeeper, the researcher sent the study information directly to them to be disseminated to potential participants. Where contacts were provided, the researcher then contacted the individuals and sent them the study information asking them to act as a gatekeeper for the study.

The researcher and academic supervisor had also made contact with a clinical reader & consultant dermatologist who was involved in organising academic meetings for a group of dermatologists from across South West Wales, prior to the start of the study. Once full approvals had been gained, the researcher attended a monthly meeting and presented potential participants with information about the research. Potential participants were invited to take part in study 2 to act as gatekeepers in recruiting patients (see chapter 5.4.2) and also invited to participate in study 3 and be interviewed themselves. All gatekeepers were asked to re-send the study information to potential participants after one month, if potential participants had not contacted the researcher after this point, it was presumed they did not want to take part and no further contact was made to recruit them.

All participants from within primary and secondary care were self-selected; participants were provided with a cover letter and an information sheet with the contact details of the research team. If a participant wished to take part in an interview, they were asked to contact the researcher directly, the researcher then contacted the participants and arranged a suitable time to conduct the interview. All participants were entered into a raffle with the chance to win a £15, £25 or £50 high street gift voucher if they had taken part and completed an interview. Participant names were written down on paper and mixed in a bowl, names were selected at random with the first, second and third names picked receiving the £15, £25 and £50 voucher respectively. The researcher then contacted the participant and sent the voucher to them either online or through the post. Recruitment took place from August 2020 and continued until June 2021.

#### **6.4.2.3 Impact of Covid-19 on recruitment**

Due to the Covid-19 restrictions, all research was postponed in March 2020, days after recruitment had officially begun. This caused a significant delay with certain health boards beginning to assess research to determine whether it would be safe to re-start the study in August 2020. When the study was approved to re-start in some health boards, it was

understood that secondary care clinicians were facing unprecedented circumstances and a number of health boards stated that although recruitment could begin again, it would be wise to wait before contacting secondary care prescribers, or to wait for capacity to be confirmed by the health board. This significantly reduced the recruitment period for this sample.

Prior to the Covid-19 pandemic, the researcher had aimed to recruit between five and seven prescribers from within each health board (a total of 35-49). As a result of the delays caused, the target sample sizes were reduced. The recruitment of prescribers across settings were significantly impacted by the challenges upon the NHS during the global pandemic. To combat the delays and disruption experienced, the researcher applied to extend the project, and this was approved for an extra 4.5 months. The researcher also widened recruitment to include primary care prescribers with dual roles in the University, in an attempt to increase the sample population.

### **6.4.3 Setting**

Interviews were originally planned to be held either face to face in participants' places of work, conducted over the phone or virtually online, depending on the preference of the participant.

#### **6.4.3.1 Impact of Covid-19 on setting**

Due to the timing of the Covid-19 pandemic and the social distancing restrictions enforced, no interviews were conducted in the participants' place of work, and instead all interviews were conducted virtually so that data collection did not require the researcher to visit hospital or GP surgery sites. Prescribers working within primary and secondary care were interviewed virtually online using Microsoft Teams, this provided additional flexibility and allowed all willing members of the sampling frame to decide whether they wanted to take part in the interview while at work or at home.

### **6.4.4 Ethical issues pertaining to subjects**

The researcher perceived no risks to the participants involved in this study.

### **6.4.5 Data collection**

The data collection methods are consistent with the methods outlined in chapter 5 (see chapter 5.4.5). The recruitment and data collection period started in August 2020; data was first collected from November 2020 and continued until June 2021.

## 6.4.6 Data processing

The data processing methods are consistent with methods described in study 1 outlined in chapter 4 (see chapter 4.4.6).

## 6.4.7 Data analysis

The data analysis methods are consistent with methods outlined in chapter 4 (see chapter 4.4.7).

# 6.5 Results

## 6.5.1 Participant characteristics

A total of 5 participants took part and completed an interview, 4 were primary care prescribers and 1 was a secondary care prescriber. As gatekeepers were involved in disseminating study information to prescribers across settings, the total number of potential prescribers invited to participate is not known and therefore the response rate cannot be accurately determined. The semi-structured interviews conducted lasted between 20-40 minutes. The interview number given to each participant, the number of years they have been registered as a doctor, the care setting in which they worked, and their gender can be seen in table 6.2.

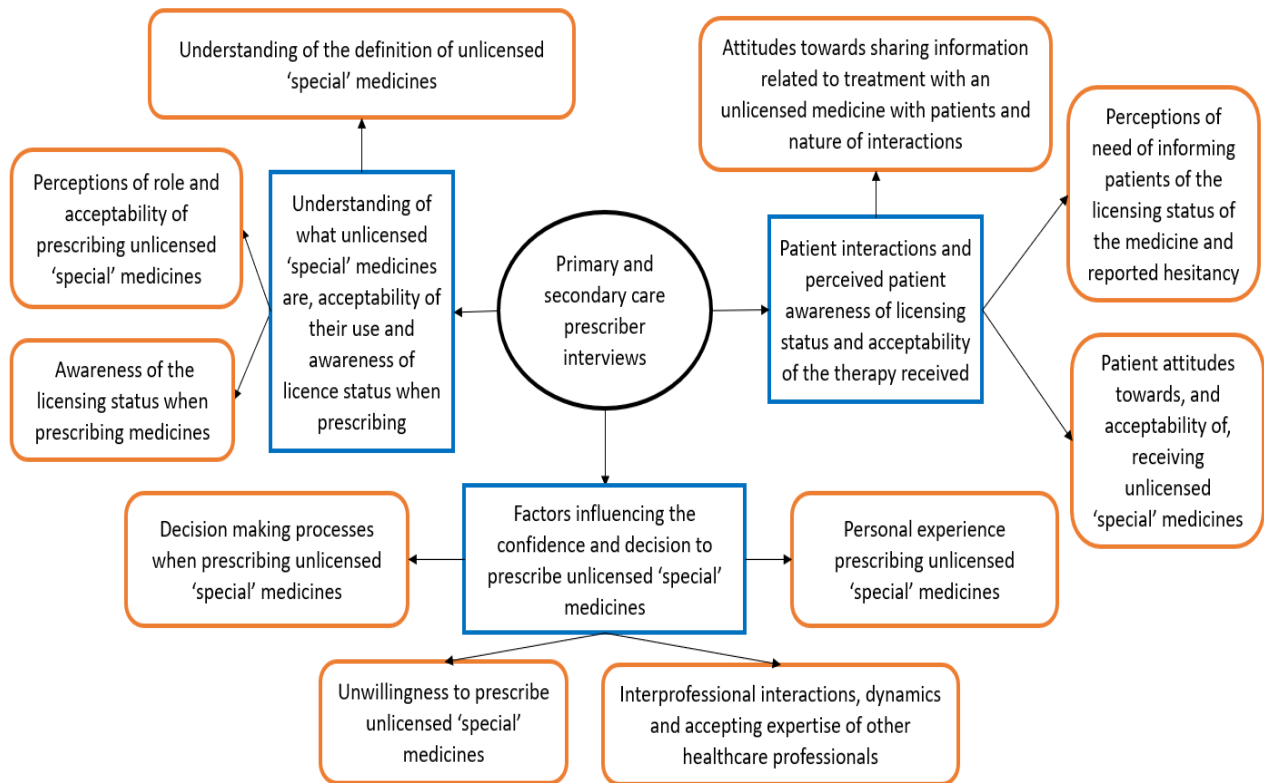
*Table 6.2 Participant characteristics in study 3 interviews with prescribers*

Interview/ participant number	Gender	No of years working as a registered doctor (yrs)	Working within primary or secondary care
INT 3.1	Male	3.5	Primary care
INT 3.2	Female	6	Primary care
INT 3.3	Female	18	Primary care
INT 3.4	Male	10	Primary care
INT 3.5	Female	16	Secondary care (Paediatrics)

## 6.5.2 Thematic analysis results

Reflexive thematic analysis of transcribed interviews was used to construct 3 themes: (1) understanding of what unlicensed 'special' medicines are, acceptability of their use and awareness of licence status when prescribing; (2) factors influencing the confidence and decision to prescribe unlicensed 'special' medicines; and (3) patient interactions and

perceived patient awareness of licensing status and acceptability of the therapy received. A graphic representation of the themes and sub-themes can be seen in Figure 6.1.



**Figure 6.1** Themes and subthemes constructed through thematic analysis of semi-structured interviews with primary and secondary care prescribers

### 6.5.2.1 Theme 1 – Understanding of what unlicensed ‘special’ medicines are, acceptability of their use and awareness of licence status when prescribing

Participants reported a lack of confidence and showed a limited understanding when defining what an unlicensed ‘special’ medicine is, and this is reflected in the lack of awareness of the licence status of medicines when prescribing. Most participants felt comfortable prescribing unlicensed ‘special’ medicines as part of their professional role, however one participant from primary care felt that this was not something that should be requested of GPs showing differing perceptions of acceptability across prescribers.

#### 6.5.2.1.1 Understanding of the definition of unlicensed ‘special’ medicines

When asked to define what unlicensed ‘special’ medicines are, participants showed a lack of certainty with varying definitions being provided, including definitions for off-label medicines.

This lack of certainty was further evidenced by some participants prefacing their responses with statements to that effect, as with:-

*“I don't know really much about it, I always think of unlicensed medicines as stuff where, they're, they're [sic] sort of, they're to be used for certain things, but if you use them for outside of that,... those specifications, then that's what I think of as unlicensed” [INT 3.3].*

One participant did attempt to define the difference between unlicensed medicines and unlicensed 'special' medicines, acknowledging the different terminology used. However, they also reflected on their own limited understanding of the nuances, showing how even when familiar with the terminology associated with different types of unlicensed medicines, the participant did not feel confident in their understanding.

*“My understanding of an unlicensed medication, so the examples that I can think of are often medications we give to children that are in regular guidelines, but aren't specifically, they don't have a specific licence for that indication or age group, typically in children, and then in terms of specials,... my understanding, again, very limited, is that it's a medication that has to be made up specifically for a patient,... because they have specific requirements” [INT 3.4].*

Another participant described how they viewed the terminology surrounding unlicensed medicines to be confusing and perceived this to also be confusing for patients. The participant did not believe the use of unlicensed 'special' medicines to be unsafe but acknowledged that the phrasing of the term unlicensed could instead imply a lack of safety, potentially perceived as such equally by patients, the public, and healthcare professionals.

*“It doesn't mean that it's unsafe, but it sounds like it is because it's a, it's a confusing term unlicensed, unlicensed, [sic]... but I think that leads to confusion not only among medical people, but also families and the public... so it seems like everything is really unsafe” [INT 3.5].*

#### **6.5.2.1.2 Perceptions of role and acceptability of prescribing unlicensed 'special' medicines**

Despite variations in understanding when defining specials, all participants but one primary care prescriber reported feeling comfortable with prescribing unlicensed 'special' medicines, as part of their role however, the confidence to do this was greater in those who prescribed unlicensed medicines more frequently compared to those who did not.

*“I feel fine use, feel fine [sic] using them [unlicensed medicines], 'cause [sic] they're not, I'm not using anything which is out of the ordinary or new” [INT 3.5].*

The secondary care clinician reported prescribing unlicensed 'special' medicines more often than primary care prescribers, and also reported higher levels of acceptability around this aspect of their role as a prescriber. Some of the primary care prescribers also reported feeling comfortable with the task of prescribing unlicensed medicines, however, two participants had differing views on how their larger role as a prescriber related to the use of unlicensed 'special' medicines.

*"I would never perceive my role being to prescribe unlicensed medicines, my role is to obviously, y'know [sic], patient-centered, trying to address their... concerns and perceived needs and, come to a shared decision about how best to do that, so as long as I feel that, and, and the patient feels that we've discussed their concerns, the benefits and the potential drawbacks or risks, adverse effects associated with the medication, and they are comfortable and confident in the medication, I feel that I have properly discharged my role and responsibility in prescribing that unlicensed medication" [INT 3.1].*

This participant decided to focus on the other aspects of responsibility when prescribing unlicensed medicines rather than on the clinical decision-making aspect that GPs are also legally responsible for. Another participant from primary care explained how they did not feel GPs should be required to prescribe unlicensed medicines in general, as the participant believed they do not have the specialist knowledge and expertise that secondary care prescribers were perceived to have.

*"I don't think GPs should be prescribing unlicensed medicines... I mean as GPs, we can't know about all the studies and all the ins and outs of the treatment for specific conditions, and so I, I do feel that should be a specialist prescription really" [INT 3.3].*

This perceived lack of expertise and knowledge led to concerns for the participant about the legal responsibilities associated with prescribing unlicensed medicines, and they described a lack of confidence in defending the prescription, if there was to be an issue.

*"If you're prescribing, if you're signing your name to the script, you are responsible, even if it's been advised by specialist and OK, you've got a bit more, to defend yourself with, but still they [specialists in secondary care], I think they should prescribe it" [INT 3.3].*

Despite the participant describing a lack of confidence and acceptability around prescribing unlicensed 'special' medicines in primary care in generals, they did describe certain scenarios in which they would be happy to prescribe unlicensed medicines. Some examples



provided included commonly used unlicensed or off-label medicines, highlighting that the individual medicine may affect acceptability among prescribers.

*“I wouldn’t say never [prescribe an unlicensed medicine] because there are cases when like, like [sic] we’ve said about with children and stuff or when it’s commonly, prescribed, and perhaps it’s just that for whatever reason, the licence hasn’t been given, or when it’s very, very slightly out of, the, the license” [INT 3.3].*

The responses from this participant highlight a variation in acceptability among prescribers but also reflect how acceptability when prescribing is impacted by the nature of, and circumstances around, the specific unlicensed medicine prescribed. This was supported by other participants who showed higher levels of acceptability for prescribing unlicensed medicines that were commonly used or familiar to them, versus newer medicines or medicines they were unfamiliar with.

#### **6.5.2.1.3 Awareness of the licensing status when prescribing medicines**

Participants reported varying levels of awareness around the licensing status when prescribing medicines, with many primary care prescribers suggesting they may not always be aware if, or when, they had prescribed unlicensed medicines. The secondary care prescriber was more aware of when they had prescribed unlicensed medicines compared to prescribers within primary care, with the participant explaining that most medicines they had prescribed were for unlicensed or off-label medicines, as they were prescribing for children.

*“Pretty much everything we use is unlicensed, (laughs) I don’t even know what is licensed, ‘cause [sic] I think most of it isn’t licensed” [INT 3.5].*

All participants from within primary care outlined concerns that they may be prescribing unlicensed medicines without consciously knowing so. This was reportedly due to prescribers not being aware or informed of which medicines are unlicensed, or which medicines have common unlicensed uses.

*“I worry that actually, we [prescribers]... we’re [sic] just unaware sometimes of whether it’s licensed or not” [INT 3.2].*

One participant described how they were not sure if the computer system used within the GP surgery highlighted when unlicensed ‘special’ medicines were selected. They explained how even if it did, they may not necessarily notice it as they prescribe so many medicines and routinely proceed through the automated checks quickly. The participant suggested that in order to ensure prescribers are made aware when they are prescribing unlicensed medicines, an alert of some kind could be introduced in the system.

*“In terms of my own experience of not being aware that what I was prescribing was unlicensed is if, is if [sic]... the computer systems that we’re using, now (laughs) I say this and I’m almost like I have to take a step back because I imagine when we are clicking the medication it probably is saying unlicensed, but there’s so many boxes that get flagged up, we just go, proceed, proceed, proceed, so yeah, some way of maybe alerting us to the fact that the medication we’re prescribing is unlicensed” [INT 3.1].*

Some participants described how this lack of awareness of the licensing status of medicines also occurred when they were requested to continue prescriptions for medicines initiated in secondary care. Participants reported that when medication letters were received from secondary care, they would not specify if the medicine being requested was licensed or unlicensed, resulting in GPs potentially continuing prescriptions for unlicensed medicines while being unaware of whether the medicine is not licensed for that use.

*“If they’re initiated in secondary care, we may not notice their licensing use, if that makes sense, so we continue prescribing but we might not notice, y’know [sic], it might not be highlighted that it’s unlicensed use” [INT 3.2].*

Participants reported varying experiences around how and why they may not be aware which medicines are unlicensed. One participant explained how prescribers may not know if a medicine is unlicensed or has unlicensed uses, if it has been commonly prescribed by other healthcare professionals for a specific condition over a long period of time. In preparation for the interview the participant had looked over their prescribing and discovered they had been prescribing an unlicensed medicine.

*“The only one [unlicensed medicine] I think, I can think that I initiate regularly in general practice is amitriptyline, for neuropathic pain... but that’s got sort of 20-year precedent for it, and it’s so, its (laughs) I didn’t even know it was unlicensed until I looked it up for neuropathic pain” [INT 3.1].*

In contrast to this, another participant described how when a particular unlicensed medicine is commonly used for a specific condition, this may actually help them to identify that the medicine is unlicensed as the prescribing practice is familiar to them and discussed among colleagues.

*“If it’s a commonly used [unlicensed medicine] then that’s how I know that it’s unlicensed” [INT3.4].*

In summary, participants reported varying levels of awareness around which medicines are considered unlicensed. However, a lack of awareness of the licensing status of medicines

was not simply down to a limited understanding on the part of the participant. Examples were provided of a perceived lack of information provided or made readily available to them, such as when receiving information from secondary care, and of lack of effective automated computer alerts that could be used to flag the licensing status when prescribing.

### **6.5.2.2 Theme 2: Factors influencing the confidence and decision to prescribe unlicensed ‘special’ medicines**

Participants discussed the factors that they took into consideration when deciding to prescribe or continue a prescription for an unlicensed medicine, which included the clinical need of the patient, the suitability of alternative products and the guidance available to them. Some participants gave an insight into what situations would result in them not being willing to prescribe an unlicensed medicine and outlined some experiences around this. All participants described a sense of professional trust towards other prescribers, pharmacists, and their health board that helped to increase their confidence when prescribing unlicensed medicines. Confidence was also increased by the participants’ own knowledge and experiences within the role.

#### **6.5.2.2.1 Decision making processes when prescribing unlicensed ‘special’ medicines**

When participants were aware that the medicine they were going to prescribe was unlicensed, they described numerous factors that impacted their decision to proceed with the prescribing or not. To assess the need of the patient, most participants considered whether licensed alternatives had been tried or were suitable.

*“I think the, the [sic] first one [consideration for prescribing] is the, the, [sic] indication, so what what's the condition? And then I suppose the other question is what licensed medications there are for that condition, and have they [the patient] tried them” [INT 3.4].*

Participants did not consider cost as a significant factor that is considered when deciding whether to prescribe an unlicensed medicine. One participant described how their rationale for cost not being a consideration was that this was superseded by the clinical need for an unlicensed ‘special’ medicine, when all licensed alternatives were exhausted or deemed not suitable.

*“If you’re deciding that [an unlicensed medicine is] what the patient needs, then often, and there is no other option, which is... more... financially sort of, sensible, then you have to, you have to take that decision anyway” [INT 3.2].*

Some participants explained how restrictions imposed by the procurement processes within the health board could influence prescribers when deciding whether to, or which unlicensed

medicines to prescribe and reflected on how cost could be a deciding factor at that level. An example of this potential influence was described by the secondary care prescriber who explained how clinicians and pharmacists within the health board discussed trying to avoid the use of liquid medicines over crushable tablets, and agreed on 'go to' medicines for specific conditions. The participant suggested that in these cases, cost may be a consideration for the health board.

*"In the health board so clinicians are involved in that discussion you know, what should we have as our 'go to' medication and yeah, cost comes into that decision as well as kind of, whether alcohol is in the solution and if we're trying to avoid liquids and trying to use Circadin tablets, crushable tablets instead" [INT 3.5].*

Another restriction on prescribing practices imposed by the health board was the formulary, with one prescriber saying they try to only prescribe medicines listed on the health board formulary, suggesting they may not prescribe unlicensed medicines even when there is a clinical need, if it is not listed in the formulary. The participant felt comfortable with this approach, as it provided them with clear guidance that they felt they needed, because of their limited experience.

*"Presumably if it's unlicensed, it's likely to not be on the health board formulary either and, you know, I do try to keep, stick to their formulary if I can as well, again partly because of, I think being a bit rusty and... yeah, probably a bit more risk averse than some of my colleagues" [INT 3.3].*

Participants from within primary and secondary care outlined the use of formularies and other guidance resources in helping to support their decision making and confidence when prescribing unlicensed medicines. Participants mentioned using the BNF, BNFc, health board formularies and NICE guidance to help guide and defend their practice and had trust in the standard of the information contained within these documents.

*"There's guidelines for most things,... how you treat things so it's often kind of through NICE or something like that, NICE guidance, and so you know you've kind of got that standard that you're working to or that guidance to back up back up your practice" [INT 3.5].*

#### **6.5.2.2.2. Unwillingness to prescribe unlicensed 'special' medicines**

One participant described why they may choose not to continue to prescribe a medicine initiated by another prescriber from secondary or primary care, whether licensed or unlicensed, specifying that they would need to know at least the dose, duration and rationale for the use of the medicine in order to feel comfortable to prescribe.

*“Whether it was licensed or unlicensed...if it [the request to prescribe] wasn't clear in terms of the dose, the duration, and the rationale then yes, I probably would refuse to, to [sic] prescribe it” [INT 3.4].*

Although not frequently occurring, some participants described circumstances in which they had been unwilling to prescribe an unlicensed medicine in the past. One participant explained how this had occurred due to their own lack of confidence in their knowledge and experience with the medicine requested by a prescriber in secondary care.

*“I definitely have the sensation of refusing [to prescribe unlicensed medicines in the past].... yeah just that feeling that it I don't, I don't [sic] have the expertise or the knowledge about the drug or, or [sic] perhaps the condition to, to [sic] prescribe it and take responsibility for it,... or know what checks I should be doing or what reviews I should be doing” [INT 3.3].*

Two participants described situations where they had been unwilling to prescribe a medicine when requested by patients who did not meet the licensing requirement, after the patient had read or heard about them in the media or online. An example of this was a request for liraglutide, a medicine licensed for use in diabetes, which had also been licensed for use in weight management if the patient meets specific requirements in 2020 and is recommended to be prescribed by a secondary care specialist in a weight management service (NICE 2020). The unwillingness to prescribe was due to the prescribers' exercising their professional judgement and considering that the unlicensed medicine requested was not necessarily the most suitable treatment for the patient, or that the patient did not meet the requirements needed to justify the use of the medicine in primary care.

*“We get requests for unlicensed medications from patients,... quite a bit... where they read stuff online... or you know they found a medication which is meant to be good for something, most recent one was liraglutide, which is used for diabetes, but also now licensed in weight loss for certain, certain people and so people do request those sorts of medications and then, but if the indication isn't there, I wouldn't [prescribe it]” [INT 3.2].*

The perceptions of inexperience or lack of confidence in prescribing reported by primary care prescribers were echoed by the secondary care prescriber, who detailed the results of an audit undertaken in the past exploring shared care arrangements. In addition to concerns already raised by primary care participants, excessive workload of GPs was highlighted.

*“5 plus years ago there was, [sic] we did an audit on... ADHD medications and why GPs weren't happy to take over shared care... and the reasons really varied, you*

*know time,... just not feeling comfortable, not feeling they had enough training... I think it's probably just not wanting feeling that they're being dumped upon I'd imagine, and just not want to take on the whole world, 'cause [sic] GPs have to do quite a lot... I'd imagine that's probably the reason" [INT 3.5].*

#### **6.5.2.2.3 Interprofessional interactions, dynamics and accepting expertise of other healthcare professionals**

Participants described how they needed the reassurance of having a sense of professional trust towards others involved in the supply chain, viewing them to have an increased knowledge and ability to determine the suitable use of unlicensed medicines. The interprofessional interactions with others such as prescribers, pharmacists and the information provided in the guidance available, helped to alleviate their concerns, as described so far, and to feel more confident when prescribing unlicensed medicines. GP participants described relying on this perceived hierarchy of knowledge and experience, and this trust was further supported through the explanation or rationale for treatment provided by secondary care prescribers in the discharge letters received.

*"If it's licensed or unlicensed, I guess... the- the [sic] specialist has made that prescribing decision so... like I said, as long as there's an explicit, that reason, rationale, duration, and dose, then I would, would [sic] usually add it to the repeat prescription" [INT 3.4].*

One participant from primary care described how the use of formal shared care protocols also helped to increase their confidence when continuing prescriptions for unlicensed medicines and viewed it as a safer process, as there were formal requirements for the healthcare professionals involved.

*"I think it would need to be a much more formal shared care protocol option [compared to a simple request to continue the prescription] for me to carry on, prescribing something that was unlicensed with specialist review... it's much safer then 'cause [sic] everyone, then it's clear what you should be doing to, to [sic] review the patient and what the risks are and, and [sic] everyone knows what they're doing." [INT 3.3].*

One participant described how pharmacists in primary care have taken on more responsibilities when patients are starting new medicines and described how pharmacists are having conversations with the patient about the newly prescribed medicines. The involvement of pharmacists working in GP surgeries was perceived as valuable by participants, seeing pharmacists as an additional resource to seek advice from, and was

reported to have reduced the workload for GPs within the surgery when dealing with patients starting new medicines and when conducting medication reviews.

*“Some pharmacists are getting involved in primary care doing that aspect [medication reviews], which is helpful, so things like that, yeah, that would be a great resource actually, more pharmacists in primary care” [INT 3.1].*

This perception that increasing the numbers of pharmacists working alongside prescribers would be a potential improvement, was reported by participants from within primary and secondary care, showing the growing reputation of pharmacists and how they are earning respect and trust from prescribers in primary and secondary care.

*“I’d appreciate a closer working [relationship] with pharmacy [staff in secondary care] ‘cause [sic] I think that, you know we need to work together, and I think everyone is so busy that we don’t work together enough... so yeah that would be ideal, but... here’s wishing” [INT 3.5].*

#### **6.5.2.2.4 Personal experience prescribing unlicensed ‘special’ medicines**

Personal experience was also seen to impact the participants’ perceived confidence when initiating or continuing prescriptions for unlicensed medicines. Participants from within primary and secondary care who regularly used specific types of unlicensed medicines for use in children reported higher levels of confidence than the other participants.

*“The majority of, unlicensed medications that I give probably are in children, and in terms of efficacy and safety, I think I’m reassured that the national guidelines have done those kind of checks, and the fact that they’ve been used for some time also reassures me the safety, and my experience, generally, the ones that I’ve given, I’m not aware of any, any [sic] problems or, or [sic] safety concerns at this stage” [INT 3.4].*

One participant from primary care described how their confidence in prescribing unlicensed medicines had developed over time leading to a reduction in them needing to use support tools such as BNF or NICE guidance to aid decision making with familiar medicines.

*“A lot of those tools you might have used a lot more when you were first starting out, and then with time they become sort of muscle memory” [INT 3.1].*

Another participant, who had very little experience prescribing unlicensed medicines reported lower levels of confidence and a reluctance to take on the responsibility associated with prescribing a medicine without a license, as they felt they would have to be too reliant on others to ensure the suitability and safety of the product.

*“I think especially as GPs, where you're prescribing such a broad range of drugs, you have to sort of, rely on the processes and rely on other people to check the safety and,... the yeah, the appropriateness of it really, and even within that obviously it can go wrong sometimes” [INT 3.3].*

Overall, participants described multiple factors that would impact their decision-making and confidence when initiating or continuing the prescription of unlicensed ‘special’ medicines. This included the needs of the patient, the guidance available from official resources, the restrictions imposed by health boards, the professional trust they felt towards other healthcare professionals and the dynamics of their relationships, as well as their own personal experience within their role.

### **6.5.2.3 Theme 3 - Patient interactions and perceived patient awareness of licensing status and acceptability of the therapy received**

Participants described having conversations with patients and discussing different aspects of the therapeutic management with an unlicensed medicine with them, including providing verbal advice during the consultation or signposting to where further information could be accessed. Some participants described discussing the unlicensed use of the medicine with patients, however, some reported a hesitancy to go into detail about the fact the medicine was unlicensed and what this meant. When discussing the perceived acceptability of the patient to be prescribed an unlicensed medicine, most prescribers reported that patients express very few concerns about the licensing status, and instead suggested that the taste or packaging of the medicine itself could have a greater impact on patient acceptability.

#### **6.5.2.3.1 Attitudes towards sharing information related to treatment with an unlicensed medicine with patients and nature of interactions**

All participants described having conversations with patients when prescribing medicines in general, and all acknowledged the importance of informing patients about the potential risks and benefits of the recommended treatment so that patients could make informed decisions.

*“I... provide the patient with the information they need to make an informed decision, and that includes the proposed benefits, potential risks, and adverse effects, and... safety netting” [INT 3.1].*

This approach was adopted for unlicensed medicines as well, and participants described discussions with patients that included details about the medicine prescribed, potential side-effects and, in some cases, the fact that the medicine was not licensed. One prescriber gave an example of how they tried to explain the licensing status to the patient.



*“I just have that discussion with them [the patient] about that, it's unlicensed, hasn't been formally kind of tested in, in [sic] a trial to be to, to, [sic] assess it, but it's standard practice and we use this on a regular basis, that kind of will be my discussion” [INT 3.4].*

Attitudes towards sharing information about treatment with ‘specials’ or off-label medicines did not vary widely and any variation in attitude was typically found to be in relation to a specific medicine and its uses. One participant described wanting to involve the patient in the decision-making, giving the patient the chance to refuse treatment with an unlicensed medicine, and explained that they would encourage patients to question the decision to take the unlicensed medicine. However, they noted that this was dependent on the medicine itself, as the participant recognised that in some cases, such as treatments for cancer, they would not take this approach.

*“I mean I probably would try and, sort of, encourage them [the patient] to question the decision to take, to be, being prescribed an unlicensed medication unless, you know I mean, if if [sic] it's cancer treatment” [INT 3.3].*

Participants described using different methods to discuss the medicine with patients, with some directly providing an explanation of why the medicine is being used in the consultation, and others also suggesting resources for patients instead, so they can access information in their own time. However, this information was usually about the condition being treated, or the medicine being used, rather than the licence status of the medication and implications of this.

*“I wouldn't probably do it for every unlicensed medication, but for some I would direct them [the patient] to the website, but not specifically for that medication, It's usually for the condition” [INT 3.4].*

The participant working in secondary care highlighted how there was a lack of information about the medicines used for children and as a result of this, they ended up relying on the information supplied by drug companies to help inform patients.

*“I think when it comes ADHD and Methylphenidate and all those kind of drugs, you know... Elvanse, methotrexate etc, then... quite a lot of supportive information is actually provided by the drug companies, for families like about the, the [sic] medicine... sometimes for teachers, for the children when they are old enough to read it, so 'cause [sic] we don't have a huge amount of health, health [sic] information, or community support for these children, we end up kind of relying on that drug companies information, which isn't ideal kind of ethically, but then if you're*

*prescribing medication anyway, it's just making the best of a non-ideal situation” [INT 3.5].*

#### **6.5.2.3.2 Perceptions of need of informing patients of the licensing status of the medicine and reported hesitancy**

Two participants described a hesitancy when it came to informing patients the medicine prescribed was unlicensed, with one participant actively saying they would not focus on the licensing status of the medicine in discussions with patients. Although participants acknowledged the importance of patient awareness and informing patients, one participant explained that their uncertainty to discuss the licensing status was due to not wanting to cause concern to patients and instead wanting to reassure them about the use of the medicine.

*“I'd have to honestly say I suspect [patients] don't [have awareness their medicine is unlicensed], and I suspect, it may be, it probably is an important part of the ethics of prescribing, when you're [prescribing unlicensed medicines], but the problem when you start saying things like 'this is an unlicensed or off label' [medicine] is it creates panic” [INT 3.1].*

A participant from within primary care expressed a perception that, when applicable, secondary care staff should have discussed the licensing status of the medicine with the patient on initiation and should have already discussed what that means as well as any potential risks.

*“If it is a drug that is a new drug and unlicensed, I mean, again, you'd hope that the specialist prescribing it would be giving [the patients] that information” [INT 3.3].*

However, this hesitancy to discuss the licensing status was reported across care settings. The participant who worked in secondary care reflected that the lack of information they provide to patients about what the unlicensed status means, is a result of their lack of confidence in their own understanding about unlicensed medicines and the associated terminology. It was also perceived that patients and families may be confused by the terminology.

*“If I'm going to start a child on an unlicensed medication, I don't actually, because most of it is, I don't actually say it's unlicensed or licensed because I think it's really confusing term” [INT 3.5].*

The confusing terminology used was also described to be a barrier in informing patients by a participant in primary care, who although was relaying the information related to licensing status, discussed that they do not emphasize the licensing status as having much importance as they find it difficult to explain.

*“Although I inform patients I don't make a big deal out of it, that it's, unlicensed use, ... I don't think, because sometimes it's quite hard to explain it to people, and therefore it becomes quite difficult” [INT 3.2].*

Another participant who did discuss the licensing status of medicines with patients also highlighted a lack of confidence in how well they had informed patients in the past.

*“I've just explained that it's out off licence 'cause [sic] it hasn't been studied in this group and, as far as we know, it's fairly safe and they've just been happy with that, but I mean, it's probably not great informing on my part” [INT 3.3].*

One participant described how their approach towards informing patients in the first place was dependent on the patient themselves, suggesting that some patients would want to know more information than others, reflecting a range of behaviours exercised when discussing the use of unlicensed medicines with patients.

*“I think it's very very dependent on the patient, and I think some patients will ask you more questions and will ask you what,[sic] will want to know more information specifically why, what does it mean by unlicensed... some people, once you've had that discussion and say that it's on kind of national guidelines, it's commonly used, are reassured and happy to, to [sic] start the medication” [INT 3.4].*

#### **6.5.2.3.3 Patient attitudes towards, and acceptability of, receiving unlicensed 'special' medicines**

Participants perceived that patients may be less concerned about the actual licensing status and more concerned about other details around the use of unlicensed medicines, such as how to use the medicine and potential side effects.

*“I think that's what [patients] they're most worried about, you know, 'what do I do if I miss it', or 'what if they have too much', 'what are the side effects', and [I have to] answer those questions, I don't think they're, too worried about the licensing [status of the medicine]” [INT 3.5].*

Participants described how patients rarely asked questions about the licensing status of their medicine and rarely raised concerns with prescribers around this, even when they had been informed.

*“So generally, I think most patients I’ve spoken to and said it’s unlicensed, I don’t think they’re particularly concerned about it, well, have not at least voiced their concerns when I’ve had those discussions” [INT 3.4].*

Participants also suggested that when they had discussed the unlicensed or off-label status with patients, as long as they provided the explanation of why the medicine was being used, patients seemed to be accepting of that.

*“I think I’ve just explained that it’s out of licence 'cause [sic] it hasn’t been studied in this group and, as far as we know, it’s fairly safe and they’ve [patients] just been happy with that” [INT 3.3].*

One participant explained that acceptability issues could be more related to the individual product, rather than the licensing status. An example of this was described for use in children, where the flavour of the medicine or even the packaging was reported to lead to a lack of acceptability.

*“Something being prescribed in strawberry flavour and [the patient] they don’t like strawberry flavour, you know all sorts [of factors can impact acceptability].....So [patients] with autism, they might not like the pack because the pack’s changed from blue writing to black writing” [INT 3.5].*

Overall, participants perceived patients to have relatively high levels of acceptability in relation to the use of unlicensed medicines and to be more concerned about how to use and manage the medicine than the licensing status itself. Participants described having conversations with patients about the use of their unlicensed medicines and recognised the importance of discussing potential risks. However, there was a hesitancy to discuss the licensing status with patients, be this because they did not want to cause concern, or because they did not feel confident in their own understanding.

## **6.6 Discussion**

The study achieved its aim to explore the views and experiences of prescribers in primary and secondary care who have experience of initiating or maintaining the prescription of unlicensed ‘special’ medicines. To the researcher’s knowledge, the results provide the first insight into this topic specifically in Wales.

### **6.6.1 The impact of a limited understanding of what unlicensed medicines are and a lack of awareness of licensing status when prescribing medicines**

Participants were asked to define what unlicensed 'special' medicines are and, although all were familiar with the use of unlicensed medicines, the responses showed varying levels of understanding with multiple definitions being provided, including definitions for off-label medicines. The variation in understanding among prescribers could be the result of the inconsistent information published about what unlicensed medicines are in the guidance available to healthcare professionals, as reported in an analysis of 52 guidelines used within the UK (Donovan *et al.*, 2018). The terminology used has been reported to be potentially confusing for prescribers in a review of the definitions and legislation associated with the use of unlicensed medicines (Aronson and Ferner, 2017) and the results of this study support this suggestion. When discussing the terminology used, one participant stated that the terms were confusing to them and perceived them to also be confusing for patients, with the term 'unlicensed' potentially leading patients to perceive a lack of safety. This is understandable as the prefix 'un-' is commonly used as negative and since the general public have limited exposure to information around the medicinal licensing process within the UK (Mukattash *et al.*, 2008), the negative familiar aspect of the word may impact public perceptions. Many participants prefaced their definitions of unlicensed 'special' medicines with statements to acknowledge their limited understanding and this shows that the prescribers in this study, from within primary and secondary care, consider themselves to not have enough of an understanding to feel confident when discussing what unlicensed 'special' medicines are.

The results highlighted how prescribers not only struggle with accurately defining unlicensed medicines, but also with recognising which medicines are considered unlicensed. All participants from within primary care described how they may not always be aware of the licensing status when they prescribe. One reason given for this was that the letters received from hospitals did not specify the licensing status of the medicine requested. The RPS (2016) outline 5 principles when prescribing unlicensed 'special' medicines (see chapter 1), the fifth of which states that prescribers should understand the need for the use of a special medicine and should be aware of the implications of prescribing a special when initiating or continuing prescriptions. The GMC (2021) also state that when using shared care agreements between care settings, clinicians should explain the indication and need for use of unlicensed medicines. Though not specifically stated, the guidance implies the prescriber taking over responsibility should be aware not just of the need and justification for the use of

the medicine, but also the fact the medicine is not licensed, in order to make an informed decision as to whether or not to take on the responsibility of initiating or maintaining therapy.

In a survey study conducted with 42 GPs and 36 secondary care junior doctors, differences were reported in what good quality discharge summaries would consist of, with over a third of GPs reporting they were not satisfied with the information provided about medication changes and over a third of hospital doctors reporting that they felt they had not received enough training on writing discharge summaries (Yemm *et al.*, 2014). A systematic review comprising of 29 studies from 11 countries including the UK, has highlighted how there are a number of risk factors associated with the use of discharge letters on patient safety, such as delays in discharge letters being sent out, and a lack of information included (Schwartz *et al.*, 2019). The review highlighted multiple issues and emphasised the importance of high-quality discharge letters. When exploring how discharge letters could be improved, interviews were conducted with 20 GPs and a focus group was conducted with 6 GPs (Weetman *et al.*, 2020), the findings further supported how discharge letters received from hospital often did not contain information perceived to be important by the participants. The authors suggested the need for the development of templates for discharge letters that can include specific factors considered to be important to GP's. A template that includes the addition of a requirement on discharge letters to categorise the licence status of the medicine requested would help GPs to become aware of this and as such, provide them with the information required to assess the clinical need and associated responsibility of prescribing unlicensed medicines. Although, this would only be an effective method when unlicensed medicines are initiated in secondary care.

When prescribing an unlicensed medicine within primary care (whether this is being initiated for the first time, or continued upon request), one participant explained how they were unsure as to whether the prescribing systems used highlighted that the medicine is not licensed, as they were used to proceeding through multiple automatic checks when prescribing, without paying much attention to individual alerts. This could have potentially negative implications for practice as prescribers do hold a legal responsibility when prescribing to ensure the use of the unlicensed medicine meets the clinical needs of the patient (GMC 2021), and if prescribers are unaware the medicine is unlicensed in the first place, this suggests they would not have been able to determine the suitability of an unlicensed medicine. The issue raised about the effectiveness of alerts in prescribing systems has been previously reported in a survey study in the UK with 220 GPs, which found that 22% of participants described frequently or very frequently overriding and not properly checking computerised drug interaction alerts, with some participants describing

how the alerts are often perceived to be irrelevant (Magnus *et al.*, 2002). Although this study was not looking at the use of unlicensed medicines, it highlighted how alert systems may not have been effective over many years. The lack of awareness of the licensing status when prescribing unlicensed medicines due to the computer system not alerting prescribers effectively has also been supported by Donovan *et al.* (2021) who found GPs, doctors with less experience and nurse prescribers had all reported experiencing this. Although the study had a relatively small sample (n=5), the findings support that prescribing systems not effectively alerting prescribers when unlicensed medicine have been selected is not only relevant to the GPs in this study, but has been experienced elsewhere in the UK and has been seen to affect the awareness of prescribers across care settings and within a range of roles.

The use of electronic prescribing systems have been found to be beneficial in reducing prescribing errors compared to when writing prescriptions; however, prescribing errors still occur such as selecting products or doses incorrectly (Donyai *et al.*, 2007). Involving healthcare professionals in the design of technology from the start, rather than only being involved in evaluating the end product, has been found to be beneficial in developing technology alongside clinical practice and supporting the success of the system within healthcare (Papoutsi *et al.*, 2021). The findings highlighted the need for an effective method that could be used to alert prescribers when they are about to prescribe an unlicensed medicine, without disrupting the workflow so that the clinical decisions associated with their use can be contemplated prior to the actual prescription being signed. As such, prescribers as end users could help to develop an electronic prescribing system that would be user friendly, and that would ensure routine alerts are distinct from alerts about the licensing status of the medicine to increase awareness when an unlicensed medicine has been selected.

### **6.6.2 Factors affecting the acceptability of and decision to prescribe unlicensed medicines**

Despite the lack of awareness of the licence status when prescribing medicines described above, all participants were aware that they had prescribed unlicensed medicines in the past, and when discussing participants' acceptability of doing so as part of their role, varying perceptions were reported. Although not described frequently, some participants did outline situations where they did not feel comfortable enough to initiate or continue prescriptions for unlicensed medicines, with one prescriber feeling that GPs should not be expected to prescribe unlicensed medicines in general. The GMC outlines that when prescribing an unlicensed medicine prescribers must be satisfied there is evidence for its safe and effective

use and take responsibility for the prescription (GMC 2021). It is important to recognise that GPs have a right to decide not to prescribe a medicine if they do not believe its use is justified, or if they do not feel confident in their own understanding and ability to safely prescribe the medicine and take on the associated responsibility. However, in cases where a GP has decided not to prescribe or continue a prescription for an unlicensed medicine a process should be in place to review the need and suitability of the medicine requested and if still deemed to be necessary, steps should be taken to reduce the chance of delays or disruption to patient care.

Previous evidence within the UK has also found GPs not always being willing to continue prescriptions for unlicensed medicines and this has been highlighted as an issue seen to delay the supply of unlicensed medicines across care settings (Husain, Davies and Tomlin, 2017; Wong *et al.*, 2006). Participants in this study provided explanations as to why they may choose not to continue a prescription for an unlicensed medicine, which included a lack of confidence on the part of the primary care prescribers around the need for the medicine or knowledge around its uses. This is supported by Wong *et al.* (2006), who conducted telephone interviews with GPs and found that a perceived lack of expertise and knowledge also led to decisions not to continue prescriptions for unlicensed medicines. Although the study only included 15 GPs and was focussed on the use of unlicensed medicines for children, the results highlight how GPs perceived limited knowledge and confidence around the use of unlicensed medicines was, and still is, a justified reason for not continuing the prescription. The findings suggest that to reduce this perception, and subsequent disruptions across care settings, further education and support may be necessary.

The perceived lack of knowledge reported by GPs in study 3 often resulted in participants having to accept and trust the expertise of other healthcare professionals in order to feel comfortable to prescribe unlicensed medicines, specifically secondary care prescribers who were perceived to hold increased knowledge and expertise. Trust has been highlighted as an important aspect across care settings when supplying unlicensed medicines (Donovan *et al.*, 2016) and the need to rely on the original prescribers' decisions has been found to affect how unlicensed medicines are administered when nurses are not familiar with the unlicensed medicines used (Haw, Stubbs & Dickens, 2015). The professional trust did help to reduce the concerns of some participants and the suggestions made to further involve pharmacists across care settings showed that participants valued working in a multidisciplinary group, wider than their counterparts in different sectors. The value of pharmacists working within general practice has been reported previously in an interview study with seven GPs who had experienced working alongside pharmacists and perceived them to hold increased expertise



around medications such as an increased understanding of drug interactions (Hampson & Ruane 2019). The positive impact of pharmacists working within general practice has also been reported by patients in a qualitative study who described an increase in accessibility to care, with pharmacists being more available than GPs, and better quality of care through the positive interactions patients had had with the pharmacists (Karampatakis *et al.*, 2021). In a systematic review of qualitative studies GPs again reported the benefits of practice pharmacists, and it was emphasised that specific pharmacist characteristics, such as being proactive and assertive, and having good communication skills, allowed the pharmacists to actively be involved in patient care by sharing their understanding of the guidance on how medicines should be used, the ability to provide medication related information to patients and staff, and were reported to be beneficial when dealing with patients with complex clinical conditions (Hurley *et al.*, 2021). Although these studies were not focused on the use of unlicensed medicines, the benefit to patient care when pharmacists were employed within GP surgeries has been well supported, and the finding that pharmacists were particularly useful when dealing with patients with complex clinical cases suggests that patients who receive unlicensed medicines would also benefit from this integration.

The NHS has recognised the divides between care settings to be a barrier to patient care and has aimed to move away from this approach and move towards providing services that are integrated (NHS 2021d). Internationally, examples have been seen of integrated care across primary and secondary care settings that allow treatment for patients with complex clinical needs to be provided more efficiently and more easily for patients (NICE 2018). When exploring integrated care programmes across eight European countries including the UK, four key success factors were identified by Czypionka *et al* (2020). These were the consideration of the mental, social and physical health of the patients, a single contact point for patients that helps to create good relationships and align services, trust between healthcare professionals that was further promoted through consistent communication, and patient involvement. The study involved interviewing large numbers of participants from 17 integrated care programmes across eight countries making the findings reliable and providing a valuable insight as it relates to ongoing practice. The findings highlight that although trust is a key aspect of good integrated care, it is a trust that has been built overtime, through experience working together and communicating effectively. The need to rely on the expertise of other healthcare professionals when prescribing unlicensed medicines as reported by participants in study 2, could be reduced through the use of an integrated care programme that would provide increased communication and improved trust between healthcare professionals as well as shared decision making.

Participants also reported accepting the expertise of those who create guidance and medicines formularies. All participants described using the medicines formularies available in order to gain more information about using specific unlicensed medicines and to support and increase their confidence in their decision to prescribe. At present, the only way prescribers can check to see if a medicine has an unlicensed status is to look up the individual medicine on the electronic medicines compendium and to review the summary of product characteristics (medicines.org.uk). The creation and use of a medicines formulary specifically for the use of unlicensed medicines has been suggested within the literature (Donovan *et al.*, 2018), a formulary like this would help primary care prescribers to be more aware of which medicines are unlicensed and could help guide the use of these medicines.

All participants explained how the individual unlicensed medicine would impact their decision as to whether to prescribe, with more established unlicensed medicines being more acceptable than newer, unfamiliar medicines, suggesting that acceptability is dependent on more variables than just the licence status of the medicine. The acceptability of participants when actually prescribing unlicensed medicines was found to be dependent on multiple factors in literature. Some of the influencing factors described in this study have been reported previously within literature conducted in the UK, such as GPs perceived lack of expertise, the positive impact of shared care protocols and advisory lists, and the individual experience of the prescriber around the use of the specific medicine being requested, with off-label medicines and frequently prescribed unlicensed medicines being perceived as more acceptable (Crowe *et al.*, 2009). Participant responses in the study by Crowe *et al.*, which involved interviews with 14 GPs and a range of other general practice staff members, revealed micro and macro level influences, such as patient need, the individual unlicensed medicine prescribed, or recommendations from within the health board or listed on the health board formulary. Both primary and secondary care prescribers reported influences at these different levels and the findings provide further evidence towards understanding the decision-making process when prescribing unlicensed 'special' medicines. These findings are further supported by Grant *et al.* (2013), who explored prescribing influences in general practice in an ethnographic study in the UK which involved observation, and nine interviews with GPs and practice pharmacists. Although the study did not look specifically at the prescription of unlicensed medicines the results along with the findings of this study, highlight the influence of both micro and macro level factors on prescribing behaviour, regardless of the licence status.

When looking at the use of unlicensed medicines, previous literature showed that healthcare professionals from within primary and secondary care have reported how the cost of the

medicine is viewed as a less important factor that impacts prescribing decisions compared to factors such as safety and efficacy (Chisholm *et al.*, 2012). This is supported by the participants in this study who described how cost was not a deciding factor for prescribers as the need for the medicine meant there would not be any alternatives available. One participant from within secondary care described instances where pharmacists and clinicians were discussing 'go to' medicines and trying to avoid the use of unlicensed liquid medicines in favour of crushable licensed tablets. Although cost could be a consideration at this level, as the high cost of unlicensed liquid medicines has been recognised when compared with tablets or licensed medicines (Lajoinie *et al.*, 2014). This practice also follows the guidance laid out by the MHRA (2014), which outlines the order in which different types of medicines should be used, starting with a UK licensed medicine, followed by a UK licensed medicine used in an off-label way, and medicines that have been licensed in another country that can be imported all being recommended before using an unlicensed 'special' medicine. Communication between healthcare professionals as described above could potentially save the NHS money if unlicensed liquid medicines are prescribed when off-label alternatives are available and could help to provide consistency in practice across prescribers. This would also be aligned with the AWMSGs five-year strategy by reducing inappropriate variation in the medicines prescribed and providing consistent and cost-effective treatments for people across Wales (AWMSG 2018).

### **6.6.3 Discussions with patients around the use of unlicensed medicines**

When participants had decided to initiate or continue a prescription for an unlicensed medicine, different methods and approaches used to discuss this with the patient were reported. Participants from within both primary and secondary care reported a hesitancy to go into detail about what the term unlicensed means, with some participants describing how they actively avoided discussing the unlicensed status of the medicine with patients. Reasons for this hesitancy included participants' own limited confidence in their own understanding of the terminology associated with the use of unlicensed medicines, as well as the perception that patients were more concerned with questions about using the medicine and potential side effects, than with the licensing status. This reluctance has been reported previously by prescribers in England accompanied by similar perceptions that discussing the licence is not as important as discussing side effects (Donovan *et al.*, 2021). Prescribers described how the reluctance to inform patients was not simply based on their own confidence and awareness, but also a result of not wanting to cause concerns to patients. This is a view that could have been informed by literature, as previous evidence

has shown that once members of the public are informed about the use of unlicensed medicines, concerns associated with their use increase (Mukattash *et al.*, 2008). However, this could also be the result of the inconsistent guidance provided to healthcare professionals on how patients should be informed. Some guidance suggests the patient should be informed of the licensing status if they are to be prescribed an unlicensed medicine (ABPI 2019)(BNF 2021b), while others suggest there are exceptions to this. For example, in cases where the use of commonly used off-label medicines, emergency medicines or where there are no other suitable treatments, some guidance indicates that providing this information may cause concerns for patients and therefore prescribers may not want to highlight the licensing status (Swansea Bay health board 2020)(AWMSG 2021).

The views that informing patients may cause concerns, or that the licensing status is not that important along with the inconsistent guidance provided, suggest that patients throughout the UK may not be fully informed when they are prescribed unlicensed medicines. Mukattash *et al* (2012) conducted surveys with a range of healthcare professionals including community pharmacists, consultant paediatricians, GPs and paediatric nurses. The results showed that although 85.4% of participants felt that parents or carers should be informed when being prescribed an unlicensed medicine, only 30.7% reported actually informing patients when this happened. Although the study focussed on the use of unlicensed medicines specifically for children, the results show that many healthcare professionals may not choose to inform patients when they are prescribed an unlicensed medicine and further highlights the need for consistent information to be created for healthcare professionals to support discussions.

The lack of consistency in the guidance provided necessitates that prescribers are left to make their own decisions about what may be considered important. This could have implications on informed consent and patient-centred care if the prescriber is determining what information the patient needs. Patient-centred care aims to involve and enable the patient in shared decision-making about their own health and treatment, to empower patients in this way and to be able to acknowledge their views and values. It is vital that patients have knowledge about their condition and treatment options available to them to make fully informed decisions (Coutler and Oldham, 2016). Informed consent is recognised as an important aspect of health care, as patients have the right to decide what treatment they receive (Welsh Government 2002). In order to achieve this, the GMC (2020b, para 3.) outline seven key principles for decision making and consent, the third of which states “*All patients have the right to be listened to, and to be given the information they need to make a decision and the time and support they need to understand it*”. However as described earlier, if the GP is unaware which medicines are unlicensed, or if they do not have consistent

guidance on their responsibility to inform the patient of the licensing status of medicines, the patient may end up not being aware; when patients are not informed that their medicine has not been licensed for the specific use involved in their treatment, they cannot fully consent to receiving it.

Patients not being informed could also have implications on continuity of care when receiving unlicensed medicines in the community, as patients have described having to take on specific strategies to ensure they can access the medicines, such as managing the lead times associated with unlicensed medicines (Husain, Davies and Tomlin, 2017). The results show the importance of ensuring all those involved across the supply chain are aware when unlicensed medicines are prescribed and highlights the need for the creation of consistent guidance for prescribers around how to inform patients when unlicensed medicines are prescribed and the creation of consistent information that can be supplied to patients when receiving unlicensed medicines. Currently a number of patient information leaflets have been created for patients receiving unlicensed medicines in the UK (NHS 2016; Medicines for children 2020), however, their content often varies. Involving patients in the co-design of information leaflets has been suggested to aid the creation of good quality patient information leaflets (Herber *et al.*, 2014; Lampert *et al.*, 2016). The need for the creation of consistent co-designed patient information leaflets has been discussed previously (see chapter 5.6.1). Additionally to increasing patient awareness, it could help to support prescribers in discussions around the use of unlicensed medicines.

#### **6.6.4 Limitations**

The researcher acknowledges many limitations faced when conducting the research. The NHS ethical approval process was time consuming and involved gaining approvals from multiple different bodies, leading to delays in the start of the recruitment process. Only interested participants would reach out to the research team, hence the researcher would not be able to know the full number of potential participants contacted, making it hard to estimate the response rate.

Despite the delay in the start of recruitment, increased efforts were made by the researcher to increase response rates, using multiple methods such as offering monetary incentives as part of a draw for participants who completed an interview and following up with the gatekeepers to send out reminders and follow-ups.

The researcher also acknowledges the small, non-representative sample included in the study and this was impacted by the Covid-19 pandemic (see Appendix 7). The sample gained primarily consisted of GPs with a dual role in academia, either contracted by the

University as research fellows or as academic fellows, and as such would inevitably produce results that are not generalisable to all prescribers. However, the findings do help to give an insight into the views of these prescribers within Wales and add to the existing knowledge around the use of unlicensed 'special' medicines in the UK.

The researcher realised that as non-pharmacist a limited insight was held in prescribing practices in general, and made every effort to prepare for interviews by looking at relevant literature (NHS 2018, RPS 2016) and discussing with supervisors and members of SSG. Despite this, it is possible that they missed cues during the interviews that referred to processes that they were not familiar with.

A final limitation to consider is the lack of understanding of prescribers of what unlicensed 'special' medicines actually are defined as, based on the definition by MHRA, meaning the discussions and experiences shared may also be related to the use of off-label medicines, making it hard to determine differences in views and experiences between the different types of unlicensed medicines.

### **6.6.5 Reflections**

The interviews conducted provided an understanding of the factors considered and perceptions around prescribing unlicensed medicines and a better understanding of the current challenges faced by prescribers. The researcher would have liked to have gained a larger sample to produce more generalisable results however, the information gained does have value and adds to the existing knowledge within the literature. The results do support previous findings that prescribers have varying perceptions of awareness around what unlicensed 'special' medicines are and their uses along with varying levels of acceptability.

When considering the recruitment strategy used, the researcher observed the value of gatekeepers during the research process. Some health board facilitators acted as gatekeepers and agreed to disseminate the study documents, however in some health boards where contacts were provided, recruitment was perceived to be a much more difficult process with emails being left unanswered and increased communication required. The researcher faced many challenges with identifying gatekeepers across Wales and reflected that the availability and acceptability of health board facilitators to get involved in ensuring information is disseminated impacted successful recruitment. The process highlighted the importance of having agreed gatekeepers lined up prior to the start of recruitment. However, the researcher recognises the lack of responses from potential gatekeepers was also impacted by an increased workload for healthcare professionals during the Covid-19 pandemic.

### **6.6.6 Conclusions**

To the researcher's knowledge, the results of this study provide the first insight into the views and experiences of prescribers when initiating or maintaining therapy with an unlicensed 'special' medicine specifically in Wales. Overall, the findings build on the existing body of literature and further demonstrate a variation in understanding and acceptability around the use of unlicensed medicines among prescribers across primary and secondary care. The results of this study provide an insight into some of the reasons for the issues seen to disrupt patient care, such as GPs not being willing to continue prescriptions or patients not being informed they are receiving unlicensed medicines. A unique finding was that one participant openly stated they find the terminology associated with unlicensed medicines confusing and this confusion directly contributed to them choosing not to discuss the licensing status of the medicines and any associated information with patients. To help reduce the chances of errors and delays in supply and disruption to patient care, it is important to build support mechanisms in the wider system, for all those involved in the patient journey. Co-designed IT infrastructure with service users, the development of an unlicensed formulary and an increased use of shared care protocols can all contribute to increasing the confidence of prescribers so that information is shared appropriately between care settings, patients are involved in decisions about their care, and NHS resources are used prudently.

## **7. Discussion**

### **7.1 Overview of chapter**

The previous study chapters have interrogated the literature in relation to the factors that can impact the patient journey and care when receiving an unlicensed medicine in the UK, and explored the views and experiences of community pharmacy staff, patients, and prescribers within primary and secondary care on the use of unlicensed medicines. This final chapter aims to provide a discussion of the key findings gained over the course of the PhD in the context of the wider literature, and to discuss the implication the findings have on practice.

The chapter consists of an initial introduction, which includes a brief background to the research topic, outlines the overall aims of the thesis and describes how these aims were met. This is followed by a review of the key findings from each area of research within the thesis (the systematic review, study 1, study 2 and study 3). A discussion around how the results of each experimental chapter relate to each other within the context of existing literature, and the implications the findings have on practice is provided. This includes a description of the recommendations for change created by the researcher and how these suggestions could impact practice and patient care.

Some reflective notes are provided on the researcher's experience of the PhD process as a whole. This includes reflections on the impact of conducting research during a global pandemic, how the evidence was collected, the use of triangulation, and how the findings have been disseminated during the course of the PhD and can continue to be disseminated in the future. Lastly, suggestions for future areas of research are provided along with a description of the strengths and limitations of the overall thesis before the final conclusions are presented.

### **7.2 Introduction**

Unlicensed medicines are used across the globe and remain an important aspect of healthcare when there are no licensed treatments available. The limited available evidence from within the UK suggests that the use of unlicensed medicines is associated with many challenges, such as a lack of availability of unlicensed medicines and delays accessing medicines after discharge (Wong *et al.*, 2006; Husain, Davies and Tomlin, 2017). The overall aim of the thesis was to gain a better understanding of the views and experiences of those involved in prescribing, accessing, supplying or receiving unlicensed 'special' medicines in Wales. This evidence was sought so as to be able to highlight strengths and weaknesses within the current approaches used within the healthcare system, and create evidence-



based suggestions for change that could improve the overall patient experience when receiving unlicensed medicines.

The overall aim of the thesis was identified originally by a stakeholder, whose organisation became the partner company to support the PhD and contributed funding towards the project. Involving stakeholders in setting priorities for research has been suggested to improve the value of the findings, as it ensures the focus of research is in line with the challenges faced or concerns described by the stakeholders who have a real-world insight into the phenomena (Grill 2021).

Understanding the views and experiences of the healthcare professionals who prescribe, obtain and supply unlicensed medicines, the patients who receive unlicensed medicines, and the context of the challenges faced by all those involved, is vital in the development of practical recommendations for change. To achieve the aim of the thesis a qualitative design with a constructivist research paradigm and a phenomenological approach was taken, semi-structured interviews were used to gain in-depth accounts of the views and experiences of the participants.

The aim of the thesis was met, and the findings gained from the systematic review and study chapters are triangulated within this chapter to provide a discussion of the findings in relation to each other and the wider literature. Triangulation can help to validate the findings of research by providing multiple datasets that offer differing views of the phenomena being studied from multiple sources (Flick, Kardoff and Steinke, 2004; Noble and Heale, 2019). Data triangulation, the approach adopted within this chapter, involves using data gained from different groups of stakeholders to compare similarities and differences in their accounts (Guion, Diehl and McDonald, 2011). Implementation science aims to use evidence-based findings and incorporate this into practice, specifically to improve the efficacy of healthcare services (Bauer *et al.*, 2015). As the researcher aimed to create evidence-based suggestions for change, consideration was given to the context of the research and involved a range of stakeholder and service users, as suggested by Prathivadi *et al* (2021). In relation to this research, the different stakeholders were the different samples gained in study 1, 2 and 3.

The themes and subthemes constructed in each experimental chapter are provided in table 7.1 as a summary of the key findings and the factors that have been reported to impact the supply chain integrated from all chapters and can be seen in figure 7.1.

## 7.2.1 Summary of key findings

**Table 7.1** An overview of the themes and subthemes constructed in each of the experimental chapters across the thesis

Themes and subthemes constructed within each experimental chapter			
Systematic review	Study 1	Study 2	Study 3
<p><b>Theme 1:</b> Prescribing of unlicensed medicines</p>	<p><b>Theme 1:</b> Requirement for additional patient responsibilities</p>	<p><b>Theme 1:</b> Awareness of licensed status and acceptability of receiving an unlicensed medicine</p>	<p><b>Theme 1:</b> Understanding of what unlicensed 'special' medicines are, acceptability of their use and awareness of licence status when prescribing</p>
<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Diversity of clinical need and impact of patient population age</li> <li>- Healthcare professional awareness of unlicensed medicine uses and guidelines and perceived acceptability of prescribing</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Patient initiated ordering of further supplies</li> <li>- Importance of patient awareness and understanding of the implications of receiving unlicensed 'special' medicines</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Lack of consistent methods used to inform patients they were receiving an unlicensed medicine and impact on patient awareness of what unlicensed medicines are</li> <li>- Acceptability of the use of unlicensed medicines</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Understanding the definition of unlicensed 'special' medicines</li> <li>- Perceptions of role and acceptability of prescribing unlicensed 'special' medicines</li> <li>- Awareness of the licensing status when prescribing medicines</li> </ul>
<p><b>Theme 2:</b> Further access and supply of unlicensed medicines after initial prescribing</p>	<p><b>Theme 2:</b> Continuity of supply</p>	<p><b>Theme 2:</b> Patient perceptions of healthcare professionals impacted by issues experienced</p>	<p><b>Theme 2:</b> Factors influencing the confidence and decision to prescribe unlicensed 'special' medicines</p>
<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Awareness and acceptability of healthcare professionals involved in further prescribing, supply or administration</li> <li>- Impact of obtaining unlicensed medicines via a manufacturer on availability in primary and secondary care</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Additional record keeping</li> <li>- Tensions within and between care settings</li> <li>- Challenges with accessibility and availability</li> <li>- perceived advantages of ordering online</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Issues faced by patients during their journey from initial prescribing of unlicensed medicines to obtaining regular supplies</li> <li>- Patient perceptions of how their care, and the responsibility for it is managed by healthcare professionals</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Decision making processes when prescribing unlicensed 'special' medicines</li> <li>- Unwillingness to prescribe unlicensed 'special' medicines</li> <li>- Interprofessional interactions, dynamics and accepting the expertise of other healthcare professionals</li> <li>- Personal experience prescribing unlicensed 'special' medicines</li> </ul>

Systematic review	Study 1	Study 2	Study 3
<p><b>Theme 3:</b> Receiving unlicensed medicines and patient care</p>	<p><b>Theme 3:</b> Influences on the confidence felt by pharmacy staff when accessing and supplying unlicensed 'special' medicines</p>	<p><b>Theme 3:</b> Strategies adopted by patients to ensure timely access and continuity of supply when receiving unlicensed medicines</p>	<p><b>Theme 3:</b> Patient interactions and perceived patient awareness of licensing status and acceptability of the therapy received</p>
<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Inconsistencies in unlicensed medicines</li> <li>- Safety issues associated with the use of unlicensed medicines</li> <li>- Patient and public awareness of unlicensed medicine use and perceived acceptability</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Ambiguity about classification and processing of unlicensed 'special' medicines</li> <li>- Information needs for safe transfer of care across settings</li> <li>- Professional trust</li> <li>- Association of confidence with experience within the role</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Adopting different channels of communication with different healthcare professionals</li> <li>- Managing and storing supplies</li> <li>- Limitations imposed by the use of unlicensed medicines on patients' personal and professional life.</li> </ul>	<p><b>Sub themes:</b></p> <ul style="list-style-type: none"> <li>- Attitudes towards sharing information related to treatment with an unlicensed medicine with patients and nature of interactions</li> <li>- Perceptions of need of informing patients of the licensing status if the medicine and reported hesitancy</li> <li>- Patient attitudes towards, and acceptability of receiving unlicensed 'special' medicines</li> </ul>

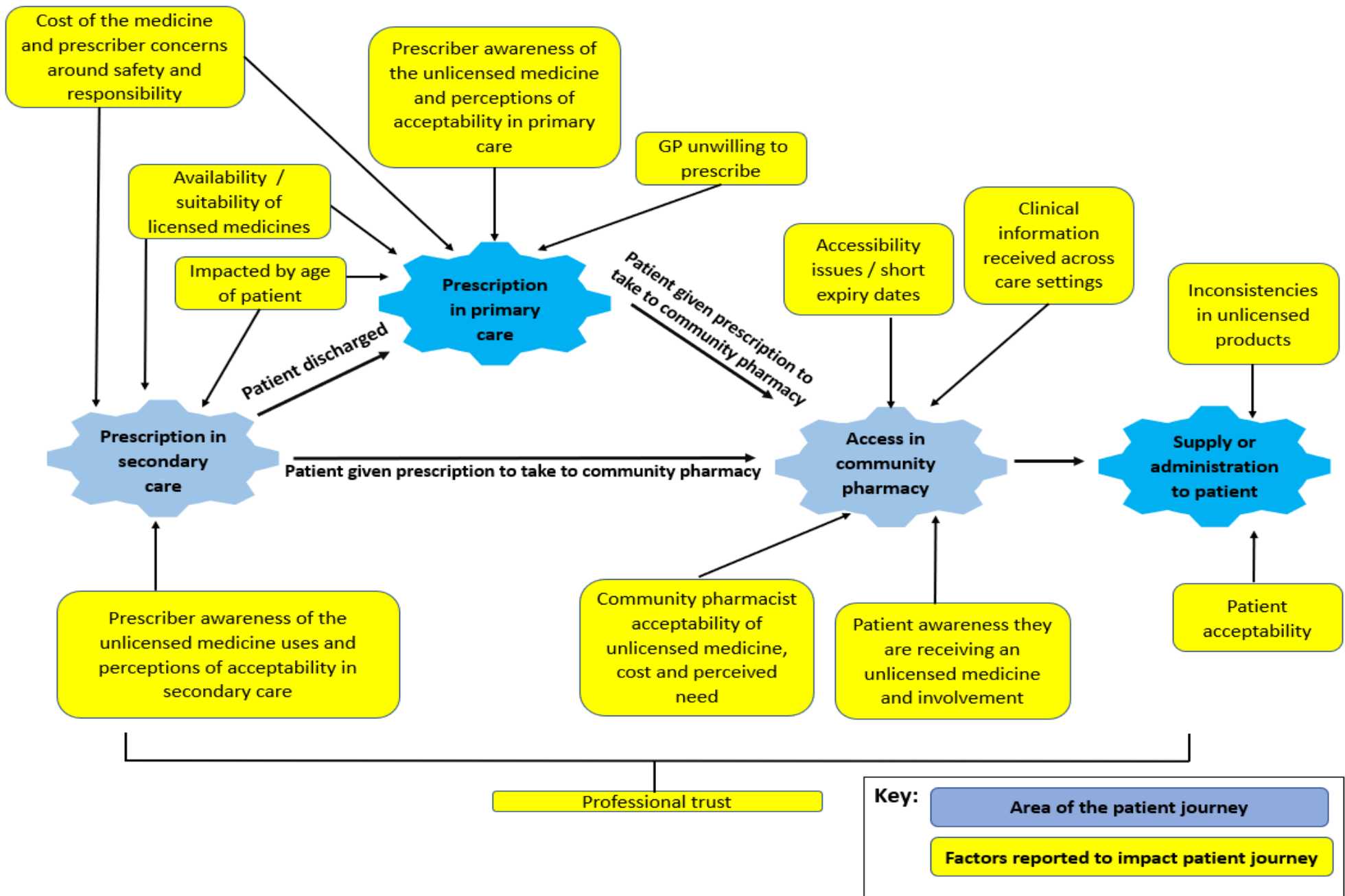


Figure 7.1 Factors impacting different areas of the patient journey

## **7.3 Discussion of Key findings**

The results gained across the thesis offer a unique insight into the use of unlicensed medicines in Wales. The systematic review was the first of its kind to explore the factors that can affect the entire patient journey when receiving an unlicensed medicine across the UK, and the individual study chapters have identified findings that have not been previously reported. This included community pharmacy staff feeling as though they need to ‘train’ their patients receiving unlicensed medicines, patient practices such as altering the doses of their child’s medication in order to manage supplies, and how prescriber confusion around the definition of unlicensed medicines and associated terminology directly led to their decision not to discuss the licensing status with patients.

The key findings gained from the systematic review and individual study chapters will be outlined and triangulated below, recommendations for change that have been created using the integrated findings will also be reported. The researcher acknowledged that as the healthcare system is complex, that a recommendation created to combat an issue described by one sample may not be practical within the wider healthcare system or may be disadvantageous for another sample, further emphasising the need for effective integration and triangulation of results in order to create recommendations that would be beneficial across the healthcare system.

Table 7.2 presented at the end of the discussion of key findings summarises the potential recommendations for change the researcher had created using the triangulated results along with their advantages and disadvantages. These recommendations are also further described when relevant in the individual discussion sections below (see 7.3.1.1, 7.3.2.1 and 7.3.3.1).

### **7.3.1 Challenges associated with the use of unlicensed medicines**

The findings from the individual study chapters and systematic review highlight specific challenges associated with the use of unlicensed medicines, from issues with the accessibility of individual medicines, to varying costs, extended lead times and inconsistencies in the medicines supplied between manufacturers.

Previous evidence has identified issues with the accessibility of unlicensed medicines for patients after discharge in the UK for example, community pharmacies being unable to identify a manufacturer to supply the unlicensed medicine required, or GPs being unwilling to prescribe the medicines (Husain Davies and Tomlin, 2017), with one study highlighting how a third of participants (total n=216) experienced difficulties accessing unlicensed medicines

in the community (Wong *et al.*, 2006). This was further supported by the findings from all three study chapters. Community pharmacy staff in study 1 described challenges sourcing specific unlicensed medicines, unexplained changes to the lead times from manufacturers and one experience where a supplier could not be identified, with the local hospital also being unable to supply the medicine leading to treatment disruption for the patient. Patients in study 2 reported difficulties and delays accessing their medicine after being transferred into the community and prescribers in study 3 reported instances where they had decided against continuing prescriptions for unlicensed medicines. Although the samples gained in the individual study chapters were small, the previous literature coupled with the findings from the thesis highlight that the challenges obtaining unlicensed medicines can directly impact patient care, and has continued to be an ongoing challenge faced by healthcare professionals and patients in the UK.

The difficulties in obtaining unlicensed medicines can be related to the nature of their manufacture. As unlicensed medicines are often made as one-off supplies they typically have short expiry dates which limits the possibility of storing supplies in community pharmacies and therefore takes increased time to obtain when compared to licensed medicines (Terry and Sinclair, 2012). Difficulties accessing medicines with short expiry dates have also been reported in relation to the treatment for cystic fibrosis, with similar reports from community pharmacists experiencing delays and interrupted supplies from manufacturers (Herbert *et al.*, 2021), showing the impact of short expiry dates on accessibility.

There are also many unlicensed medicines that are not manufactured in the UK and may need to be imported from other countries, again increasing the time needed to obtain these medicines. The MHRA (2015) highlight how unlicensed medicines are often imported, for example when shortages of licensed medicines are experienced. The MHRA (2019) have also provided evidence that between October 1<sup>st</sup> and Dec 31<sup>st</sup> 2018, a total of 22,646 notifications for the import of unlicensed medicines were recorded in the UK, and although not all of these may have been approved, the evidence highlights the frequent perceived need to import unlicensed medicines and further supports the potential for delays when obtaining unlicensed medicines in the UK.

Another challenge associated with the manufacture of unlicensed medicines is the increased costs and variation in formulations available. Unlicensed medicines can be manufactured with differing excipients when making the same medicine (Rawlence *et al.*, 2018), and as unlicensed medicines are made in smaller quantities than licensed medicines and prices cannot be advertised, manufacturers are responsible for determining the cost of their

products (Griffith 2013). These factors often result in unlicensed medicines being much more expensive than licensed medicines, which led to the creation of the drug tariff (Griffith 2019)(see chapter 1). The variation in excipients used between manufacturers does not only result in varying costs but also varying formulations of the same medicine. Evidence from the systematic review has shown there are variations in unlicensed formulations when manufactured and therefore supplied to patients (Mulla *et al.*, 2007). The findings from study 2 show that patients do experience these variations in Wales, with one patient describing how they had received three different brands of their unlicensed medicine over three months, and were aware of the large variations in cost between brands. This variation in the formulations available will inevitably increase the chance of patients receiving differing medicines. This can occur as when patients are discharged from secondary care into primary care, community pharmacies are not required to use the same manufacturers as the hospital had, which can result in differing medicines being supplied to patients across care settings (Bourns 2017). However, supplying differing formulations may also have an impact on the clinical efficacy of the medicine and patient safety (see 7.3.4).

The challenges faced when obtaining and supplying unlicensed medicines suggest the need for careful considerations and strategies to ensure consistency in supply, and reduce the chance of delays for patients. For this to happen healthcare professionals would need to have a good understanding of these issues and the impact they can have on patient care, while integrating care and putting the patient at the focus to ensure the patient receives continuous care without any unnecessary variation in the medicine received, or delays to treatment.

### **7.3.1.1 Recommendations**

There is little that can be done about the extended lead times and short expiry dates of unlicensed medicines as it would be impractical to produce them in commercial quantities to increase availability as demand for these medicines are not as high when compared to licensed medicines and therefore would not be cost-effective and would increase waste. However, there are a number of approaches that could be adopted to reduce the variation in formulations and cost.

Evidence has shown that costs to the NHS are saved when hospitals continue to supply unlicensed medicines to patients in the community through a scheme involving a delivery service (Terry *et al.*, 2012). This finding suggests that costs to the NHS could be reduced if hospitals agree to continue supplying unlicensed medicines to patients in the community and could increase the consistency of the medicines supplied. However, the study only included

the supply of 67 medicines for just over three months and so further research is needed to validate the findings and determine if this is a practical option for the future.

As there are a lack of pre-specified agreements between hospitals and community pharmacies when patients receiving unlicensed medicines are discharged, creating agreements for the use of unlicensed medicines and providing associated suppliers could help to reduce the number of differing formulations supplied to patients and ensure consistency. A final recommendation that has already been acknowledged and is ongoing is the addition of more unlicensed medicines to the drug tariff to continue reducing costs. The benefit of the drug tariff on the cost of unlicensed medicines has already been highlighted within the literature identifying reductions in the cost of drug tariff and non-drug tariff specials being recorded since the drug tariff was created (Chaplin, 2014) (See 1.3.4 for further information about how the drug tariff or hospital supplies can save spending on 'specials').

### **7.3.2 Inconsistent guidance and limited understanding of how and when unlicensed medicines should be used.**

The challenges associated with the use of unlicensed medicines as described above emphasise the importance of healthcare professional understanding of how and when unlicensed medicines should be used. However, findings from the studies conducted within the thesis and from within the literature highlight the limited understanding of healthcare professionals around the use of unlicensed medicines across all care settings, and the impact this can have on patient care. A limited understanding of healthcare professionals was seen to impact practice in many ways.

The terminology associated with the licensing status of medicines has been suggested to be confusing for prescribers within the UK (Aronson and Ferner 2017), and a narrative review conducted by Mason, Pirmohamed & Nunn (2012) revealed how the definitions provided for off-label and unlicensed medicines vary within the literature. This variation in defining and understanding what unlicensed medicines are, was directly reflected by prescribers from within secondary and primary care in study 3, who provided a range of definitions, with some openly stating they were not confident in their understanding around what the different terms mean. Differences in definitions were also reported among community pharmacy staff in study 1, and by patients in study 2, reflecting variations in understanding of what defines an unlicensed 'special' medicine between a range of healthcare professionals and patients.

However, it was not just the definition of unlicensed medicines that healthcare professionals across studies 1 and 3 reported a limited understanding of, but also how and when specific unlicensed medicines should be used. As unlicensed medicines are not solely related to any



specific condition, speciality or population group, but rather used across all ages and a range of clinical areas, it is difficult for any healthcare professional to have a complete understanding of when unlicensed medicines are the most suitable options and the range of indications they can be used for. The systematic review identified specialist prescribers who had prescribed a medicine for a use in which the manufacturers had advised against, as they were not aware of the specific uses for different indications (Howell and Madej, 1999), and nurses who had administered unlicensed medicines suggesting they did not feel confident enough to challenge the doctors' decisions (Haw, Stubbs & Dickens, 2015)(see chapter 2.4). In one study, only 17% of prescribers (total n=249) reported being very comfortable in relation to prescribing unlicensed medicines (Chisholm, 2012). This variation in confidence around how and when unlicensed medicines should be used was also reported by community pharmacy staff in study 1, who described a need to rely on the perceived expertise of prescribers to have determined the suitability and safety of unfamiliar unlicensed medicines. However, prescribers in study 3 also described a lack of confidence associated with their own understanding of unlicensed medicine use, and this was reported to directly impact GPs' decisions to prescribe. When GPs had decided not to prescribe an unlicensed medicine, this often led to delays for patients accessing medicines, as described by community pharmacy staff in study 1 and patients in study 2. GPs who decided not to prescribe unlicensed medicines have also been seen within the literature (Husain, Davies and Tomlin, 2017) with one of the reasons for this decision being a lack of confidence or feeling as though they did not have enough experience to prescribe for children with complex clinical conditions (Wong *et al.*, 2006). The study explored the requests for unlicensed medicines to be continued in the community from a specialist children's hospital that typically deals with rare or complex conditions and therefore the views of the GPs may not be generalisable to requests for all unlicensed medicines. However, this perceived lack of expertise was also reported by GPs in study 3, highlighting that prescribers in primary care may not feel confident enough to prescribe some unlicensed medicines, and this continues to be a barrier to continuity and supply in the UK.

There are a myriad of influences that were seen to impact the decision to prescribe unlicensed medicines in study 3. This included the individual medicine itself, their own personal experience, the use of shared care agreements and advisory lists, and guidance or recommendations from within the health board. These influencing factors were also identified in the systematic review by a study exploring GPs decision making around prescribing specialist medicines (Crowe *et al.*, 2009) highlighting a range of micro and macro level influences on prescribing behaviour. Although the study only involved 14 GPs, wider literature not specific to the use of unlicensed medicines has also highlighted the influence of

micro and macro level factors (Grant *et al.*, 2013), showing that prescribing decisions are not dependent on the licensing status of the medicine (see chapter 1.5.1 for further information on prescribing influences).

The limited understanding of prescribers was also found to contribute to the reluctance described in study 3 around informing patients of the licensing status of unlicensed and off-label medicines when they were prescribed. The reluctance of prescribers to inform patients was also reported by Donovan *et al.*, (2021), revealing that prescribers in other areas of the UK may also not be confident in their understanding and ability to discuss the use of unlicensed medicines with patients, directly impacting practice. Some prescribers in study 3 outlined how their reluctance to discuss the licensing status of the medicine with patients was also the result of not wanting to cause concerns for patients and one prescriber perceived the terminology used to imply a lack of safety. This is a justified perception as the systematic review highlighted how members of the public's concerns over the use of unlicensed medicines for children significantly increased once informed about their use (Mukattash *et al.*, 2008). Furthermore, one patient in study 2 also expressed how the term unlicensed would make them question if the medicine was safe.

The limited understanding and confusion around what unlicensed medicines are, or how and when they should be used could be the direct result of the inconsistent guidance supplied to healthcare professionals. Donovan *et al.*, (2018) conducted an analysis of 52 guidance documents on the use of unlicensed medicines that were in use within the UK, and inconsistencies were found in relation to what unlicensed medicines are. This highlights the need for clear and consistent guidance to be created for healthcare professionals to support the use of unlicensed medicines.

Guidance also varies on how to inform patients when unlicensed medicines are prescribed, with some guidance stating prescribers should always ensure patients are aware (BNF 2021b) and others stating that if this information may cause concerns that the prescriber may decide to not inform the patient of the licensing status (AWMSG 2021). This provides an explanation of the reports of some prescribers who described actively avoiding discussions around unlicensed medicines with patients in study 3, but also has implications on informed consent and patient-centred care (see 7.3.3) The findings highlight the need for consistent guidance and support for healthcare professionals when prescribing, obtaining or supplying unlicensed medicines and also highlights the need for consistent information for patients so that they can be informed of the challenges associated with accessing unlicensed medicines without causing concerns.

There are other inconsistencies in clinical guidelines that have been identified within the literature, for example differences in treatment intervals recommended for colorectal cancer (Molenaar, Winter and Slooter, 2021) and differences in recommendations in guidance for how to evaluate and manage hypertension were also identified (Alper *et al.*, 2019). It has been suggested that guidelines with conflicting information can be confusing for healthcare professionals in the UK (Hitchen, 2007), and further supports the need for clear and consistent guidance to be available for healthcare professionals to support practice and increase confidence.

Overall, the evidence shows that the terminology associated with unlicensed medicines is confusing for healthcare professionals and there is inconsistent information provided in guidance documents. This has led to a limited understanding and reduced confidence around using unlicensed medicines with many healthcare professionals reporting gaining confidence through practical experience in study 1 and study 3. The link of growing confidence with experience has been found elsewhere in literature, for example pharmacist prescribers have also reported building confidence over time as they gain more experience within the role, in a survey conducted by the GPhC (2016) and nurses working in neonatal care were also found to report higher confidence levels with increased experience (Banaka *et al.*, 2016). As the reported lack of confidence and limited understanding was seen to impact practice there is a clear need for increased training or support for healthcare professionals around the use of unlicensed medicines. In the UK, undergraduate medical schools do not have a specific curriculum but have guidance on learning outcomes that should be met (Sharma, Murphy and Doody, 2019), which can be ambiguous. As a result of this, differences have been reported between medical schools on how clinical and non-clinical topics are taught such as, ethics and law (Preston-Shoot and McKimm 2010), dementia (Tullo and Allan, 2011) and the management of burns (Zinchenko, Perry and Dheansa, 2016). It has also been found that the approach to assessments varies between medical schools in the UK, in type and intensity, and this variation is correlated with postgraduate performance (Devine, Harborne and McManus, 2015). The findings highlight that newly qualified doctors may start their role with varying levels of confidence, and could further explain the variation in acceptability of prescribers around the use of unlicensed medicines reported in study 3.

### **7.3.2.1 Recommendations**

There is a clear need for consistent information and terminology to be decided upon and provided in guidance documents, including definitions of the different types of unlicensed medicines, and how to effectively inform patients when they have been prescribed an unlicensed medicine without causing concerns. Increased education and consistent

information for healthcare professionals about the use of unlicensed medicines would help to reduce the need to rely on the expertise of others and increase confidence and understanding. In order to achieve this, information could be created and disseminated to healthcare professionals in a number of ways, including creating information to be sent out to current healthcare professionals across care settings to give an update with clear information to help increase understanding, such as a key fact update sheet or CPD event. Involving stakeholders in the development of guidelines has not only been seen as useful when creating good quality guidance that is trustworthy within the literature (Qaseem *et al.*, 2012), but also provides benefits when it comes to implementation (Petkovic *et al.*, 2020). As such, a range of stakeholders could be involved in the creation and dissemination of updated guidance documents to ensure readability and usefulness for the end users.

As the current guidance available contains inconsistent information, updated guidance would be more beneficial if it could be disseminated to a range of healthcare professionals using a top-down approach, making the AWMSG an ideal organisation to achieve this. The researcher and academic supervisor have completed a project proposal form which has been submitted to the AWMSG. The project would aim to create guidance for prescribers across primary and secondary care settings throughout Wales that can provide clarification around understanding what the different classifications of unlicensed medicines are, understanding responsibilities throughout the different stages of the prescribing journey and key steps to be taken when prescribing or transferring care. Consistent information could also be created and incorporated into educational programmes for healthcare professionals to ensure an increased level of understanding of newly qualified staff. Within this process, it would be imperative to gain contributions from key stakeholders during curriculum development, as it has been shown to improve its relevance to users and ensure quality (Belita, Carter and Bryant-Lukosius, 2020).

### **7.3.3 Lack of integrated and patient-centred care**

The challenges associated with the use of unlicensed medicines and the limited understanding of healthcare professionals around how and when unlicensed medicines should be used, was further exacerbated by a lack of integrated and patient-centred care.

Patients often have complex clinical cases that may require treatment within primary and secondary care and across different clinical areas, and as healthcare professionals may have differing levels of access to information about what other healthcare professionals have done, there are clear inefficiencies and challenges that could be overcome by integrating care (NICE 2018). Integrated care aims to support patients throughout their journey and to reduce the divides across the different healthcare settings (NHS 2022a). This is in line with

the AWMSGs five-year plan which recommends providing seamless care for patients and plans to do this by creating “an All Wales Homecare prescribing and administration chart”, which will help to provide consistent care after discharge from hospital (AWMSG 2018 pp. 6).

Despite the introduction of the local health boards in Wales in 2009 (Lewis 2015), it is clear from the findings in the study chapters that there is a detachment between community pharmacies, other primary care and secondary care settings, and this lack of integrated care can have implications on continuity when patients receiving unlicensed medicines are transferred from one care setting to another. The divide between primary and secondary care has been present within the NHS since it originated (Greengross, Grant, and Collini, 1999) and increases the chances of miscommunications or inadvertent changes to medicines when patients transfer across settings which can impact patient safety (RPS 2012) (see 7.3.4).

This detachment was also seen to translate to differences in understanding of the responsibilities between healthcare professionals and assumptions about practice across settings, with one GP in study 3 perceiving that prescribing specials should not be expected of GPs and that secondary care prescribers who were perceived to hold increased knowledge should be responsible for this practice. This perception has also been reported by GPs in relation to oral health with some GPs feeling as though they are already spread too thin across specialities and that those with more specialised knowledge in dentistry should be responsible for oral care (Ahluwalia, Crossman & Smith, 2016). Another study found that pharmacists felt that it was the prescribers’ responsibility to inform the patient if the medicine was unlicensed (Donovan *et al.*, 2016) despite the GPhC (2018b) stating that pharmacists are also responsible for gaining informed consent. The findings and wider literature show that there are differences in perceived responsibilities, and this coupled with the lack of integrated care has been found to lead to tensions among healthcare professionals.

Tensions were identified in the study chapters, for example as described by community pharmacy staff in study 1, when they were unable to obtain and supply an unlicensed medicine for the patient when the locum GP had decided they did not want to continue the prescription, or feeling as though they were not supplied with enough clinical information across care settings. Despite calls to increase the discharge information transferred to community pharmacies (Hodson *et al.*, 2014), in practice the information provided to community pharmacists on medication changes after discharge has been found to be inconsistent, and of poor quality (Urban *et al.*, 2013). One advancement in pharmacy

practice in Wales that aimed to improve medication safety during transfer of care, and improve quality of communication of medication changes, is the DMR service. The service was introduced in 2011 and is using a two-part approach. The first involves the community pharmacist reviewing the medicines prescribed when the patient was in hospital and comparing this to the medicines prescribed by the GP after discharge to identify any differences, the second stage involves the pharmacist having a discussion with the patient around any issues identified in the medicines prescribed or discussions around the use of the medicine that may support adherence (Hodson *et al.*, 2014), (see chapter 1.5.3 for further information on the use of the DMR service in Wales).

A similar approach in England is the use of the discharge medicine service (DMS), which was only recently introduced as an essential service in February of 2021. This involves sending referrals to community pharmacy so that they can compare the medicines received prior to hospitalisation with medicines prescribed at discharge and when prescriptions are continued in primary care (PSNC 2022b; NHS 2022b). Based on a previous evaluation exploring the association of the DMR service with reduced hospitalisations in Wales (Mantzourani *et al.*, 2020), the potential benefits of the DMS have been discussed within the literature, and similar results were suggested (Wickware 2021).

Services like the DMR and DMS may improve transfer of care and information transfer between care settings. This is important as in a systematic review conducted in 2019, collaboration between community pharmacists and GPs was described as suboptimal, and this was found to be influenced by negative views held by GPs about pharmacists, such as questioning their motivations in relation to cost (Urban *et al.*, 2008 as cited in Hindi, Jacobs and Schafheutle, 2019).

Tensions have also been reported in the literature between GPs and hospital doctors, with secondary care doctors discouraging trainee doctors from the profession of general practitioners and using the hierarchical structure to imply general practitioners are substandard (Rimmer 2017). Tensions between these group have also been suggested to directly impact practice and patient safety (Johnston and Bennett, 2019). Although these tensions were not centred around the use of unlicensed medicines, the findings show that the existing tensions can impact practice and further stresses the need for integration, respect and understanding of the different roles held between healthcare settings.

In relation to the use of unlicensed medicines GPs have previously expressed concerns around taking on the legal and clinical responsibility for specialist prescribing that was initiated by another doctor in secondary care, feeling as though they should not be held responsible for someone else's prescribing decision, especially in an area where they have

little experience (Horne *et al.*, 2001). This perception was also highlighted in study 3 with one GP stating they would prefer if secondary prescribers, who hold increased expertise would maintain the responsibility for supplying unlicensed medicines. This is a justified concern and reason to decide against prescribing an unlicensed medicine, as prescribers are held legally responsible for any prescription they sign and are recommended not to sign a prescription for an unlicensed medicine unless they feel comfortable that the medicine is the most suitable option and has enough evidence to support its use (GMC 2021) (see chapter 6 for further information about GP rights and responsibilities and the impact of medico-legal concerns on practice).

However, when disagreements occur over the responsibility to prescribe, this can leave patients without the medicine they need (NHS 2018). Evidence gained from the study chapters supports how this lack for integration results in delays or disruptions when healthcare professionals across settings do not agree on if they are comfortable to prescribe the unlicensed medicines. Experiencing delays and disruption in this way led to one patient in study 2 perceiving GPs as less caring and less responsible. This was a direct result of the care they had received as their GP had decided against prescribing the unlicensed medicine on numerous occasions, which resulted in delays for the patient when accessing their medicine, negatively impacting the doctor-patient relationship. This coupled with the secondary care doctor having to write letters to repeatedly ask the GP to continue the prescription to ensure continuity and a note on medicine box actually stating “*as prescribed by the endocrinologist*” implied the GP was not responsible to the patient. This perception has been supported within the literature by other patients receiving unlicensed medicines describing how the GP role was viewed as simply signing the prescription (Husain, Davies and Tomlin, 2017). This is also perceived by the general public who have described GPs as “*the middle man*” and thought that care would be of higher quality in hospitals (Biddle *et al.*, 2006 pg.928; MacKichan *et al.*, 2017 pg.9-10). The findings highlight the importance of informing patients about GP rights and responsibilities so that the relationship can be improved, and the importance of integrated care to ensure patients experience fewer delays. Although not focussed on the prescribing of unlicensed medicines, an example of how this information can be supplied to patients has been provided by the BMA (2004), who created guidance which outlines why some GPs may decide against prescribing a medicine that others may feel comfortable prescribing.

Prescribers in primary care, in study 3, also reported receiving limited or no information when medicines were requested from hospital, although this differed to the limited clinical information described by community staff, and instead related to a lack of specification when the medicine was unlicensed. This led to a lack of awareness of the licensing status of

medicines requested for continuation within primary care on the part of some the GPs with one GP explaining how they had looked through the repeat prescriptions they had signed in preparation for the interview, and discovered they had been prescribing unlicensed medicines without realising. The lack of awareness of the licensing status when prescribing unlicensed medicines was not only due to the lack of information provided across care settings, but also as a result of the prescribing software not effectively alerting prescribers when unlicensed medicines were selected. Similar findings were reported by Donovan *et al* (2021), where prescribers also acknowledged that the prescribing software may not alert them to the licensing status when unlicensed medicines are selected, and therefore they too may be unaware when they had prescribed unlicensed medicines. Issues have also been reported in the wider literature that show other types of alerts on prescribing software are not effective and can be viewed by prescribers as irrelevant (Magnus, Rodgers and Avery, 2002). This suggests there needs to be a more effective way to alert prescribers when unlicensed medicines have been selected. If prescribers are not aware when they have prescribed unlicensed 'special' or off-label medicines, not only would they be unable to effectively inform patients of the licensing status of the medicine, but they may also be inadvertently not complying with the record keeping requirements (see chapter 1.3.3).

Despite the tensions described above there was a desire reported for more integrated working within the study chapters. Pharmacists and prescribers in study 1 and 3 reported how when they had experienced more integrated care such as good quality information transfer between settings or the use of shared care protocols, their confidence in their own practice increased. Patients in study 2 also highlighted the need for further integrated working citing many of the issues with access they had experienced being related to differences in acceptability among healthcare professionals in different care settings or a lack of communication across care settings. Within the literature doctors have expressed the need for integration between primary and secondary care in the UK, believing that the barriers faced between care settings can negatively impact on the quality of care provided to patients (BMA 2018). The use of integrated care models has been studied within the UK and elsewhere in a systematic review, which found improvements in quality of care, access to care and patient experience (Baxter *et al.*, 2018). Although the review was not focused on the UK specifically, the evidence supports the use of integrated care and identifies its benefits in different healthcare systems around the world. More specifically in Wales, examples of integrated and seamless care have been reported by the Welsh NHS confederation (2018) (see chapter 6 for further information about the pilot studies included) and the healthcare professionals involved have outlined the perceived benefits of this approach including increased communication but also an improved understanding of



individual roles, highlighting how integrated care may help to reduce the tensions described above.

The current lack of integration results in a lack of patient-centred care with one patient in study 2 not being informed of the licensing status when they were prescribed an unlicensed medicine for their child, and who only became aware of this when they were invited to participate in the study, and prescribers in study 3 reporting a reluctance to inform patients. This is supported by the findings of the systematic review which highlighted varying rates in how often patients were informed of the licensing status when prescribed an unlicensed medicine (Ghosh *et al.*, 2010; Mukattash *et al.*, 2011). However, a good example of patient-centred care was reported by the community pharmacy staff in study 1, who described a balance that was needed when informing patients their medicine was unlicensed without causing concerns. This approach included informing patients their medicine is unlicensed or off-label, explaining what this means and the need to order the medicine in advance of when further supplies were needed, all while allowing patients to discuss any concerns that may arise. This was reported to lead to good relationships between the community pharmacy team and their patients, and further supports the need for clear and consistent information to be created for patients so that they can be informed about the use of unlicensed medicines in general and the implications of this without causing concern. The content around risk presented in patient information leaflets have been found to increase concerns for patients and can contribute to non-adherence (Herber *et al.*, 2014). To combat this, involving patients in the design of information leaflets may help to improve the content and can help to reduce concerns (see chapter 5 for further information about current patient information leaflets available and the benefits of patient involvement in design).

The lack of patient-centred care could also explain why patients who receive unlicensed medicines are required to take on increased responsibilities, as described by community pharmacy staff in study 1, and manage access across care settings as described by patients in study 2. Patients describing taking on specific strategies to manage the ordering of and access to unlicensed medicines has also been reported in England (Husain, Davies and Tomlin, 2017). The evidence from the study chapters and the wider literature has shown that patients across the UK may be faced with a need to manage access to unlicensed medicines across care settings, or else put themselves at risk of delays or treatment disruption. This finding further emphasises the importance that patients are informed not only of the licensing status of their medicines, but also the implications this has on accessibility.

However, the need for patients to take on increased responsibilities to ensure they could access their unlicensed medicine on time resulted in specific concerns for patients in study 2 around being unable to access supplies when needed. This was because they had experienced not being supported when delays occurred between settings, having to contact healthcare professionals in secondary care themselves to ensure they could access further supplies.

The findings from study 2 highlight that patients' acceptability of receiving an unlicensed medicine was impacted by a cost benefit analysis between the perceived need for the medicine and the potential risks. Participants described strong perceptions of need and few concerns around the risk of receiving an unlicensed medicine, either stating they had trust in their doctors or viewing the risk of not taking the medicine as being much higher than receiving an unlicensed medicine. No participants reported non-adherence or any intention to stop adhering to their current treatment plan, in fact the most evident concern described by participants in study 2 was around being unable to access their unlicensed medicines, and this is in line with the necessity-concerns framework (Clifford, Barber and Horne, 2008).

However, evidence identified in the systematic review highlighted how some members of the public have stated they would refuse to accept an unlicensed medicine if prescribed instead of a licensed alternative (Chisholm 2012). This could be the result of a perceived lack of need, as members of the public may have differing perceptions than patients who have complex clinical conditions that have been impacting their quality of life or threaten their long-term health, and who may have tried a range of licensed alternatives. It is acknowledged though that, as the sample in study 2 was small, further research would be needed to determine adherence rates and behaviours for patients receiving unlicensed medicines in the UK.

One patient in study 2 described further difficulties in accessing their unlicensed medicine and described how their need for the unlicensed medicine had led to reduced work opportunities as they had been informed that the medicine would only be supplied through one community pharmacy when they had requested for it to be changed to another location, leaving the patient to feel as though they were unable to move locations for any reason. This experience supports the lack of patient-centred care that patients receiving unlicensed medicines may face as advice from the BMA (2021) states that patients should be able to choose which pharmacy they receive their medicine from.

Overall, the lack of integrated and patient-centre care has been seen to directly lead to delays and results in patients feeling as though they are not supported. The lack of integrated care, coupled with healthcare professionals limited understanding around the use

of unlicensed medicines and the challenges associated with the use of unlicensed medicines were all seen to impact the patient journey and care when receiving unlicensed medicines in Wales, and each has its own implications on patient safety.

### **7.3.3.1 Recommendations**

It is clear there is a need for increased integration across care settings to allow for improved patient-centered care for patients receiving unlicensed medicines. However, the need for integrated care is not specific to the use of unlicensed medicines and has been recognised by the NHS, with the recent introduction of integrated care systems in England and the plan to further integrate care systems in Wales (see 1.6). Shared care protocols have been found to increase confidence in GPs when prescribing as described in study 3, but also within the literature (Crowe *et al.*, 2009). If protocols were created specifically for the use of unlicensed medicines this would increase prescriber confidence and may reduce decisions not to prescribe and associated delays to patient care.

There are a number of initiatives in practice that are aimed at ensuring continuity of care across settings or increasing information transfer. An example of this is the use of summary care records (SCR) in England, in which an electronic record contains information on the medicines the patient is using and any allergies they may have (Department of Health and Social Care 2011). However, SCR are generated using information from the GP records (PSNC 2022c). A more recent initiative in Wales is the creation of a national patient record system for patients with eye conditions that will support patients within primary and secondary care settings by allowing ophthalmologists in both settings to be able to access clinical information (Welsh Government 2021d). Initiatives like this, that aim to ensure information is shared across care settings could not only help to improve continuity in relation to the supply of unlicensed medicines in Wales but could also be adopted in other areas of the UK where similar issues accessing unlicensed medicines after discharge have been experienced.

In order to increase awareness of the licensing status when prescribing unlicensed medicines, access to clinical information should be available for all healthcare professionals involved in prescribing or supplying the medicines. A requirement to state the licensing status in discharge letters or medicine requests, or a flagging system to alert other healthcare professionals involved in the patient journey could be enforced that would reduce the lack of awareness seen in study 3. The use of electronic discharge letters (e-DALs) has been shown within the literature to improve continuity of care between secondary and primary care settings, (Mantzourani, Way and Hodson, 2017). Electronic DALs could be further utilised by integrating information about the medicine being supplied, including

licensing status, indication and duration. This information could be added into e-DAL in the free text box when DMRs are conducted or in the notes when the DMS service is used in England and could be completed by the initiating prescriber to increase information sharing and ensure awareness of the licensing status across care settings.

Another approach to targeting this is the involvement of prescribers in the co-design of updated prescribing software to ensure medicines are marked as unlicensed in the drug dictionary when prescribers select a medicine to prescribe. This would reduce accidental prescribing of unlicensed medicines as seen in study 1 and help to increase awareness of the licensing status across care settings. However, this would be a time-consuming process and would incur costs in order to replace prescribing software, so may not be practical.

Formularies like the BNF and BNFc are regularly used by community pharmacy staff and prescribers (study 1 and 3) and help to increase the confidence of those prescribing and supplying unlicensed medicines. The creation of a formulary for unlicensed medicines has been suggested elsewhere within the literature (Donovan *et al.*, 2018). As the drug tariff already contains a list of unlicensed medicines (see chapter 1.3.4) and a recommendation to increase the number of unlicensed medicines listed has already been suggested (see 7.3.1.1), a tailored formulary for unlicensed medicines could be created by updating the drug tariff. A formulary like this could be used across the UK and could contain different sections for the different types of unlicensed medicines. In addition to reducing costs and improving the consistency of supplied medication, an unlicensed formulary could also help to increase the confidence and awareness of the licensing status when prescribing (see impact of the drug tariff and advisory lists in 7.3.1 and 7.3.2 respectively).

Lastly, patients have a clear need to be informed when they receive unlicensed medicines, not only so they are able to provide informed consent but also, so they are aware of the challenges faced when accessing unlicensed medicines and the need to order in advance. The project proposal created and submitted to the AWMSG also aims to create a consistent patient information leaflet, which can be supplied to patients when first prescribed an unlicensed medicine and can be co-designed with patients (see chapter 5 for further information on patient information leaflet design). This will help to increase awareness in patients and provide guidance on how to manage the extended lead times and short expiry dates often seen with unlicensed medicines. As highlighted in 5.6.1, across the UK many different organisations have created patient information leaflets on the use of unlicensed medicines. Therefore, this approach could also be implemented in other areas of the UK to create a nationwide or a UK-wide information leaflet to ensure patients receiving unlicensed

medicines are informed in a consistent manner and are aware of the differences in accessibility.

### **7.3.4 Risks to patient safety**

The use of unlicensed medicines is complex and the evidence from the study chapters and systematic review have highlighted how patient safety is impacted by many factors. The evidence gained from the systematic review has highlighted how it is not all unlicensed medicines that are associated with increased risks to patient safety, but that select unlicensed medicines for specific uses, for example Fentanyl (Bellis *et al.*, 2013), oncology medicines (Bellis *et al.*, 2014) and benzo-diazepine-type medicines (McAuley *et al.*, 2015), may impose increased risks of ADRs. However, there are also many unlicensed medicines that have been used over long periods of time and that have been found to be effective without actually having been through clinical trials. An example of this is the use of specials in dermatology, where multiple creams or ointments have been used for over half a century with their long-term use providing empirical evidence in relation to the safety and efficacy of the medicines, reducing the need to run clinical trials (Buckley, Root and Bath, 2018). This further reinforces the need for healthcare professional understanding to ensure unlicensed medicines are not used for indications that may be unsafe, but can also explain the variation in confidence and acceptability described by healthcare professionals in relation to differing unlicensed medicines. However, the findings from the individual study chapters (study 1, study 2, and study 3) highlight how patient safety can also be impacted by other factors.

#### **7.3.4.1 The impact of challenges associated with the use of unlicensed medicines on patient safety**

The short expiry dates and extended lead times associated with unlicensed medicines mean patients may be left without medicine if their supplies are lost or destroyed. This knowledge resulted in patient concerns in study 2 around accessibility and the development of potentially unsafe strategies to ensure they did not miss treatment, examples included syringing the medicine off the floor when dropped, or buying supplies privately and using past its expiry date when delays were experienced accessing supplies through the NHS.

The finding from study 2 that a patient was given their medicine from the community pharmacy past its expiry date, further emphasises the challenge of supplying medicines with short expiry dates and the important role community pharmacy staff play in ensuring the medicine is suitable and safe for use. Community pharmacy staff in study 1 also described the challenges related to managing the short expiry dates of unlicensed medicines which meant they could not be stored within the pharmacy and resulted in the need for patient involvement. This challenge can be impacted by the individual medicine prescribed as many

medicines have large variations in terms of expiry, for example some medicines used to treat cancer have been found to expire after only 24 hours (Gilbar, Chambers and Gilbar, 2017). Previous evidence has shown that other patients have also reported being supplied medicines after their expiry date, with one medicine being dispensed three months after it had expired (Franklin and O'Grady, 2007) providing evidence that this challenge is not unique to the use of unlicensed medicines. This can have a direct impact on patient safety as using medicines past their expiry date, may be unsafe or limit the efficacy of the product (NHS 2020), and although not all medicines are unsafe to use after the expiration date, certain medicines such as insulin and liquid antibiotics have been highlighted within the literature as medicines that should not be used after they have expired (Tull 2018). The findings highlight again how it is certain individual medicines that may impose increased risks to patient safety if used after its expiration date and healthcare professionals need to provide clear information to patients around if their medicine, unlicensed or licensed, is safe to use after the expiry date or if it would be safer to miss a dose until further supplies can be accessed.

The various formulations available for unlicensed medicines was highlighted within the systematic review as a key issue when accessing unlicensed medicines across care settings, and was also experienced by pharmacists in study 1. The finding from study 2 that one patient had received varying brands of their unlicensed medicine provides evidence that the issue of varying formulations is experienced in Wales as with other areas of the UK. An example of this is provided by Husain, Davies and Tomlin (2017), where GPs were reported to have written prescriptions for different formulations of unlicensed medicines than had been prescribed to the patient previously. While community pharmacies do not have to use the same manufacturer as initiating hospitals had done, and can choose suppliers based on the best price available (Baird and Beech, 2020) this can have implications on patient safety. The findings from the systematic review found that differing formulations of unlicensed medicines are not necessary equivalent to the licensed versions or other unlicensed formulations (Mulla *et al.*, 2011), with pharmacists reporting inconsistent bioequivalence in the formulations received depending on the manufacturer (Venables *et al.*, 2015). This further emphasises the importance of reducing the cost of unlicensed medicines so that decisions on suppliers can be based on providing continuity with the formulation supplied previously.

#### **7.3.4.2 The impact of inconsistent guidance and limited understanding on patient safety**

Inconsistent guidance can result in inconsistent practice and when healthcare professionals have a limited understanding and have to rely on the expertise of others as described above,

this increases the chances errors could slip through, or disruptions can occur when varying levels of acceptability impact continuity between settings. The limited understanding can lead to unsafe or unnecessary uses as described in the survey with specialist prescribers, where a medicine was prescribed for an indication the manufacturer had stated the medicine should not be used for (Howell and Madej, 1999), and in study 1 where pharmacists had reported prescribers selecting unlicensed medicines by mistake. The lack of understanding and confidence of prescribers can also lead to delays or disruptions between settings when GPs do not feel confident enough to prescribe, as described in study 1, 2 and 3, and as highlighted in the systematic review (Wong *et al.*, 2006,) and it has been found that prescribers may lack familiarity with the guidance available (Chisholm, 2012). In order to improve patient care and patient safety, further information and support should be provided to healthcare professionals across care settings on the use of unlicensed medicines. The RCGP have been recommending that GP specialist training be extended from three to four years, as overtime they have been expected to cover a range of clinical areas (RCGP, 2012, RCGP,2017). This further reinforces the need to ensure trainee doctors are provided with enough education and support to feel confident in the practice that will be expected of them once qualified, to improve patient safety.

The inconsistent information about how to inform patients could also impact patient understanding and the awareness of the need to take on increased responsibilities when accessing unlicensed medicines, which could result in treatment delays and therefore risk to patient safety if the patient does not manage ordering effectively. Community pharmacy staff reported the importance of patient awareness to ensure they can successfully take on the increased responsibilities required of them, and the potential risk to patient safety if this is not managed effectively.

#### **7.3.4.3 The impact of a lack of integrated/patient-centred care on patient safety**

Many organisations have placed a focus on improving patient care through the development of integrated care systems, or highlighted the need for further integration across healthcare settings to provide seamless care, including the AWMSG's 5 year plan (2018), the Welsh Government (2021b), and the NHS long term plan (2019c). This is because a lack of integrated care poses many risks to patient safety as it has been recognised that as patients transfer from one care setting to another there is a need for coordination to ensure that clinical information is not lost (WHO 2016).

However, the findings from the study chapters highlight how patients receiving unlicensed medicines in Wales may not be experiencing integrated care between settings, as the difficulties reported by patients when accessing unlicensed medicines after discharge

reported in the literature (Wong, 2006; Husain, Davies and Tomlin, 2017) still appear to be ongoing. Patients are also not receiving patient-centred care as highlighted with one parent not being informed their child was receiving an unlicensed medicine (study 2). When patients are not informed, they cannot be involved in the decision-making process and therefore cannot provide informed consent. However, this also implies that they will be unaware of the need to manage extended lead times and this can impact patient safety if delays or disruption occurs.

The lack of integrated and patient-centred care resulted in patients in study 2 needing to manage their own treatment across care settings. When delays or disruption occur between settings patients were left to chase up healthcare professionals to ensure they could access their treatment (study 2). Experiences of delays resulted in one patient relying on private care when treatment could not be accessed on time from the NHS, however this resulted in costs to the patient, suggesting that if the patient could not afford to buy their unlicensed medicine they may have experienced treatment disruption more frequently and therefore increased risks to their safety. Evidence from the wider literature has also shown how patients accessing private care experience shorter times associated with receiving medical care, and increase eased in accessing appointments (Owusu-Frimpong, Nwankwo and Dason, 2010). The findings suggest that although there was an overall sense of appreciation for the care the NHS provides reported by patients in study 2, there are specific limitations that may impact patient safety if not addressed.

Overall, patient care and safety when receiving unlicensed medicines was found to be impacted by a range of factors including the understanding of healthcare professionals around how and when to use unlicensed medicines, healthcare professionals perceptions of acceptability on the use of unlicensed medicines, the availability of the medicine needed and the support provided to patients when accessing unlicensed medicines. In light of the findings the researcher has included a number of recommendations that could be adopted to improve the patient experience and reduce the issues reported by the participants within the study chapters. These recommendations will need to be disseminated effectively if they are to contribute to any real world change, and will need to be further discussed with stakeholders to determine their feasibility.



**Table 7.2.** Potential advantages and disadvantages of recommendations made

Factor to address	Recommendation made	Advantages and disadvantages
<p>Limited understanding of healthcare professionals (HCPs) around what unlicensed 'special' medicines are – inconsistent terminology.</p>	<ul style="list-style-type: none"> <li>• Consistent information and terminology to be decided upon by AWMSG/AWTTC.</li> <li>• Guidance document produced AWMSG/AWTTC to include:               <ul style="list-style-type: none"> <li>○ definitions of the different types of unlicensed medicines</li> <li>○ clear description of healthcare professionals' responsibilities across the supply chain.</li> </ul> </li> <li>• Guidance shared via a key facts update sheet or CPD event.</li> </ul>	<p>This would help to increase understanding among healthcare professionals and reduce confusion. Multiple participants from within primary, secondary and community pharmacy agreed on the need for further information and training. Increased education and consistent information for health care professionals about the use of unlicensed medicines would help to reduce the need to rely on the expertise of others and increase confidence and understanding. It was agreed the most effective way to create and dissemination on a national level was through the AWMSG/AWTTC.</p>
<p>Lack of confidence when prescriptions for unlicensed medicines are transferred between care settings.</p>	<ul style="list-style-type: none"> <li>• Produce a shared care protocol for use when prescriptions for unlicensed medicines are to be transferred from secondary care and continued in primary care.</li> </ul>	<p>If shared care protocols were created specifically for the use of unlicensed medicine this could increase prescriber confidence and may reduce refusals and associated delays to patient care.</p> <p>However, this may not be practical for use with all unlicensed medicines, as many are used commonly and do not cause prescriber's concern. Shared care protocols for the use of unlicensed medicines could be created and used for specific unlicensed medicines or when prescribers may not have experience prescribing the unlicensed medicine.</p>
<p>Limited confidence in when and how to use unlicensed medicines.</p>	<ul style="list-style-type: none"> <li>• Produce a formulary for unlicensed medicines containing different sections for the different types of unlicensed medicines/ specials/ off-label/ common/ less common.</li> </ul>	<p>Formularies like the BNF and BNFc are regularly used by prescribers and community pharmacy staff and help to increase the confidence of those prescribing and supplying unlicensed medicines. A formulary for unlicensed medicines could be built using nationwide data of the unlicensed medicines used over the past few years.</p>
<p>Awareness of licensing status when</p>	<ul style="list-style-type: none"> <li>• A requirement to state licensing status in discharge letters or medicine requests, or a flagging system to alert other healthcare professionals involved in the</li> </ul>	<p>This would help increase healthcare professionals' awareness of the licensing status across care settings and could be incorporated into guidance.</p>

Factor to address	Recommendation made	Advantages and disadvantages
prescribing unlicensed medicines.	patient journey could be enforced that would reduce the lack of awareness seen in study 3.	<p>A standardised template could be created with information to accompany recommendation in secondary care for prescribing of an unlicensed medicine (including specification of the licence status, indication, why a licensed product was not appropriate, expected duration of prescribing, date of review of need for the product).</p> <p>An alternative method to increase prescriber awareness of the licensing status is the addition of a requirement to outline the licensing status, indication and duration of unlicensed medicines within free text boxes in e-DALs.</p>
	<ul style="list-style-type: none"> <li>Prescribers as co-designers could help to update prescribing software.</li> </ul>	<p>There are two main prescribing software used within practice EMIS and Vision, instead of re-designing prescribing software, the organisations could be contacted and medicines could be marked as unlicensed in the drug dictionary when prescribers select a medicine to prescribe, this would reduce accidental prescribing of unlicensed medicines and help to increase awareness of the licensing status.</p>
Hesitancy of prescribers to inform patients of the licence status of their medicine.	<ul style="list-style-type: none"> <li>Prescribers need clearer consistent guidance on when and how to inform patients they are being prescribed an unlicensed medicine, as current guidance varies in this area.</li> <li>A consistent, standardised information leaflet could be created for patients to be provided with prescriptions for unlicensed medicines, explaining what an unlicensed medicine is, why patients are being prescribed these medicines, cost, shelf-life and an emphasis on the differences in lead times when accessing unlicensed medicines.</li> </ul>	<p>The creation of a consistent information leaflet for all patients receiving unlicensed medicines could increase patient awareness of the licensing status while addressing concerns that may arise.</p> <p>This could also help with prescribers' reluctance to discuss unlicensed status as a leaflet can provide information around this.</p> <p>This would also support patients in accessing unlicensed medicines in the community by providing guidance on how to manage extended lead times.</p> <p>It was agreed the most effective way to create and disseminate on a National level was through the AWMSG/ AWTTTC.</p>
Challenges impacting continuity of care when receiving unlicensed	<ul style="list-style-type: none"> <li>Hospitals could have specific agreements with specials suppliers, we know prescribers make decisions about 'go to' treatments and this could go a step further to</li> </ul>	<p>As community pharmacists can choose which suppliers they use, and some chains have specific suppliers already selected this may be impractical to enforce.</p>

Factor to address	Recommendation made	Advantages and disadvantages
medicines in the community.	include associated suppliers for commonly used unlicensed medicines to ensure consistency of formulations across care settings and reduce the chance of delays or disruption when patients are discharged.	<p>However, a recommendation could be added to guidance “from a professional perspective you should be trying to ensure continuity of care for your patients”.</p> <p>When prescriptions for unlicensed medicines are transferred into the community acceptance and agreements between GPs and community pharmacies could be gained prior to the patient being transferred to reduce risk of disruption during transfer.</p>
	<ul style="list-style-type: none"> <li>Evidence has shown that when hospitals continue to prescribe to patients in the community, this does help to reduce costs for the NHS and could be a method adopted.*</li> </ul>	<p>Could be an approach used for the very complex or rare cases where the unlicensed ‘special’ medicines may be difficult or costly to source in the community (for example if there are few manufacturers that make the medicine). Less suitable for commonly used off-label medicines.</p>
Strategies to ensure supply.	<ul style="list-style-type: none"> <li>Patients need reassurance around accessing supplies, in cases where delays, disruption or loss of medication occurs, individual advice could be supplied to patients about missing/altering doses and about emergency supply processes.</li> </ul>	<p>Healthcare professionals would be in a good position to discuss information with patients.</p> <p>Gaining advice from healthcare professionals could help to increase patient safety if delays or loss of medication occurs. This may also make the patient feel more prepared and supported if supplies are lost and reduce concerns.</p>

\* Unlicensed ‘special’ medicines are not made in large quantities and are therefore more expensive to manufacture. Suppliers may have to do a range of tests on the products they manufacture, to be able to decide what price they want to sell the medicines for. This often leads to large variation in prices among suppliers and can lead to increased costs to the NHS (see 1.3.4). Continuing to manufacture an unlicensed ‘special’ medicine in a hospital pharmacy setting may be cheaper than the costs associated with external suppliers.

### **7.3.5 Sharing of triangulated results**

In order to improve the strength and applicability of the recommendations created the researcher sought to gain feedback from the steering group, which comprised of a number of healthcare professionals within different roles (see chapter 3) and were therefore capable of providing different perspectives on the recommendations created and could provide guidance on the best way to support real-world change.

The researcher arranged two steering group meetings whereby the results of the studies were outlined and the potential suggestions for change, along with the advantages and disadvantages created by the researcher were discussed. The SSG helped to contextualise the suggestions made, along with the advantages and disadvantages presented.

#### **7.3.5.1 Actions taken after sharing of results with SSG**

In order to best utilise the recommendations and create real-world change it was agreed with the SSG that creating consistent information would be the first step, and as the AWMSG is a national organisation this would be most suitable approach. To achieve this the researcher and academic supervisor created a project proposal as described in 7.3.2.1 and 7.3.3.1 and this was submitted on the 28<sup>th</sup> October 2021. The project proposal has been reviewed and accepted by the AWMSG on the 19<sup>th</sup> January 2022 and at the time of writing (26<sup>th</sup> January 2022), a meeting has been arranged with representatives of the AWMSG to discuss this further.

## **7.4 Reflective notes**

### **7.4.1 Reflections on PhD process and experience**

When looking back over the course of the PhD as a whole, the researcher is grateful for the many opportunities that arose to develop their skills and gain experience working with a range of academic staff, healthcare professionals and members of the public. The researcher felt that during the PhD, not only were they able to develop practical experimental research skills, but also their own self-confidence and perceived ability to be able to provide a meaningful contribution to the existing knowledge base.

#### **7.4.1.1 Reflections on methods used**

The researcher viewed the benefit of using semi-structured interviews to be evidenced in the in-depth and detailed results gained from each participant, A challenge faced during data collection is when patients asked clinical questions in interviews. However, the researcher and academic supervisor had predicted this experience may happen, and had discussed how these questions should be managed. As such, when the researcher was asked about a

patient's medication and what the licensing status meant, the researcher outlined the definition that had been agreed upon and included in the patient information booklet and suggested that if the patient had any specific questions about the use of unlicensed medicines or about their specific unlicensed medicine, that they should contact a member of their healthcare team. However, a range of challenges were faced that were seen to impact the methods used and overall research experience, as a result of the Covid-19 pandemic.

#### **7.4.1.2 Reflections on triangulation**

The value of triangulation has been discussed previously (see 7.2). This is important when exploring the complex use of unlicensed medicines that involves a range of stakeholders across multiple care settings. The need for triangulation was evidenced by the differing suggestions provided by participants that were not always compatible for participants in other areas. An example of this was a suggestion made in study 3, where one participant explained how it would be helpful if the community pharmacy dispensing the unlicensed medicine could alert the GP to the fact the medicine was unlicensed. However, this would not be beneficial to community pharmacy staff and patients as if the medicine was identified by the GP to be wrong or unnecessary at this stage, not only would it cause an increased workload while the prescription is corrected, but may also lead to delays or disruption for the patient. By gaining insights from a range of stakeholders, recommendations can be created that are practical and beneficial to all those involved. The researcher also recognised the value of triangulation when comparing similarities described by differing stakeholders, such as the limited understanding of the terminology associated with unlicensed medicines being described by prescribers in primary and secondary care, highlighting this issue was identified for doctors across care settings and within different roles. Triangulating the evidence gained from different stakeholders allowed the researcher to feel more confident in the recommendations created.

#### **7.4.1.3 Reflections on dissemination**

The researcher took many steps to disseminate the findings of the research. Firstly, during the course of the PhD, the researcher maintained regular contact with members of the SSG. This involved periodically updating SSG members about the progress of the project through the use of newsletters (see Appendix 5) and presenting the findings obtained at SSG meetings, and collaborative meetings with the partner company. Creating newsletters and presenting the findings at meetings allowed the researcher to explore and gain experience using different writing and presentation styles and it was perceived that these approaches did help to maintain engagement with the SSG members.

The researcher saw the benefit of having an engaged multidisciplinary SSG and found the guidance and feedback they provided to be invaluable as members were able to support the set-up of the study and could offer different perspectives to help contextualise the findings. The researcher believes the advantage of such a group can also be seen in the improvements made to the individual interview schedules used and when exploring the recommendations for change which led to an increase in the confidence of the researcher.

The researcher presented findings from the thesis at a number of events including, Cardiff University postgraduate research days, in which the researcher was awarded a poster prize in 2019. A poster was also created and presented in the Health Services Research & Pharmacy Practice Conference (HSRPP) in 2020. The researcher took part in a number of events held at Cardiff University's doctoral academy where the research was presented through talks. This included the KESS 2 winter networking event in 2019 and the three minute thesis competition in 2020. In line with KESS 2 requirements the researcher also took part in the KESS 2 grad school, a three-day residential event where the researcher was able to present their research in a range of formats, and share time with other research students. These experiences seemed daunting at the start of the research process to the researcher who does not like to be the centre of attention, however, over the course of the PhD and with further exposure to presenting and sharing findings, the researcher not only found their self-confidence had increased, but also found an enjoyment in sharing the research findings with others. As the researcher had always desired to be able to have a career in which they could use scientific methods to contribute towards real world change and ultimately be of use to society, the experience of doing a PhD has been overwhelmingly positive and has encouraged the researcher to want to continue being involved in research or the reviewing of evidence within the healthcare sector.

The evidence gained from study 1 was used to produce a journal article which was accepted for publication in the international, peer reviewed online journal, integrated pharmacy research and practice, and further steps have also been taken to utilise the thesis findings, in a project proposal application to the AWMSG. Creating the journal article gave the researcher the opportunity again to write in a different style and contribute to the existing literature and the project proposal being supported by the AWMSG has further supported the benefit and value of the research findings. Overall, the researcher viewed dissemination not only to be an effective way to share results but also as a method of highlighting the value of the findings.

## 7.5 Recommendations for further research

Although the findings of this thesis help to add to the existing knowledge around the use of unlicensed medicines within the UK and provide a detailed insight into the participants, due to the small sample sizes included, further data could be collected to gain more views and experiences of those involved in prescribing, supplying and receiving unlicensed medicines. Further research could also involve obtaining the views and experiences of a range of other stakeholders, for example pharmacist independent prescribers and nurse prescribers. These healthcare professionals have experienced additional training and have been found to show statistically significant differences in the tasks they undertake when making prescribing decisions, one example being that pharmacist prescribers were more likely to provide treatment options to patients than nurse prescribers or GPs (Weiss *et al.*, 2015). The findings suggest that prescribers within different roles may use varying approaches when making prescribing decisions and therefore may have differing views or approaches when prescribing unlicensed medicines. As the evidence from the study chapters showed differences in perceptions between the healthcare professionals involved, to gain an even wider perspective on the use of unlicensed medicines across care settings, exploration into the views and experiences of all healthcare professionals who are involved in prescribing, obtaining, and supplying unlicensed medicines could be undertaken, as this may highlight further facilitators or challenges associated with the use of unlicensed medicines .

The findings highlight that patients may have concerns when first informed about the use of unlicensed medicines and a variation in how patients are informed was identified. As such, further research could be conducted into the views of the patients with more of a focus of adherence beliefs and behaviours, to determine if like the patients in study 2, the perception of need outweighs the potential risk for all patients. Specific frameworks have been used within healthcare research, such as the theoretical domains framework to highlight the influences on healthcare professional behaviours when implementing evidence-based recommendations for change (Atkins *et al.*, 2017), or the COM-B behaviour change wheel which explores how behaviour is impacted by capability, opportunity and motivation (Michie, Stralen and West 2011). Conducting research while incorporating behaviour change frameworks could be used in the future to better understand the facilitators or barriers to implementing the recommendations created for change within practice or to better understand adherence related behaviours of patients, so that both groups can be supported.

The survey developed from the findings of study 1 could be validated and disseminated to community pharmacy staff across the country to provide further evidence on a national level. A number of the recommendations provided by the researcher (e.g. agreements created

across care settings before the patient is discharged or the use of an unlicensed medicines formulary) could be used to develop pilot studies to determine the impact of these suggested approaches on practice.

In order to identify further areas of research of importance to those involved a research priority setting study could be conducted with a range of stakeholders including policy makers, healthcare professionals and patients to identify areas where all groups feel further research could benefit practice or the patient experience. An example of a research prioritisation exercise has been conducted by Laughlin, Spence and Noyes (2020) in relation to kidney disease and the study found that involving a range of stakeholders enabled the identification of shared research priorities that were perceived to be needed to support the services being offered for patients with kidney disease. In this way stakeholders could provide key areas they perceive need to be targeted or would benefit from further research to support the use of unlicensed medicines in the UK and improve the patient experience.

## **7.6 Strengths and Limitations**

The researcher acknowledges there are many strengths and limitations of the overall thesis. Each of the experimental chapters outlined and addressed their associated strengths and limitations (see chapters 2,4,5,6) therefore the overall strengths and limitations of the thesis will be outlined below.

### **7.6.1 Limitations**

The researcher viewed the biggest limitation of the research to be related to the delays caused by the Covid-19 pandemic. This led to the postponement of non-essential research and resulted in a reduced timeframe for recruitment even with the project being extended. This contributed to the small sample sizes gained within the study chapters which is another factor that limits the generalisability of the findings, however the findings do appear to support previous findings from within elsewhere in the UK which increases their validity and adds to the evidence base.

Another limitation that could impact the interpretation of the results was the inconsistent definitions used within the literature and provided by the study participants, in relation to unlicensed, specials and off-label medicines. This means the results may not have distinguished the different challenges faced when prescribing, supplying or accessing different types of unlicensed medicines and further emphasises the importance of deciding upon consistent terminology so that the differences can be further explored.



Lastly, the researcher does not have a clinical background and does not have experience as a stakeholder in the use of unlicensed medicines, and therefore lacks insight into the practice of prescribing, obtaining and supplying medicines. As such, the researcher tried to mitigate this through discussions with academic supervisors and members of the SSG who provided a valuable insight which helped to contextualise the findings in relation to practice.

### **7.6.2 Strengths**

The findings of the thesis contribute to the existing literature. The systematic review collated and explored the available evidence in relation to the use of unlicensed medicines and provided the first review to explore the factors that can impact the patient journey and patient care when receiving unlicensed medicines in the UK. The review highlighted many factors seen to impact the patient journey and care and also highlighted that there were no studies solely conducted in Wales. As such, to the researcher's knowledge, the study chapters provide the first insight into the views and experiences of the different stakeholders specifically in Wales.

The methodology is a particular strength of the thesis, the researcher took many steps to produce a replicable and reliable thesis outlining in detail the methods chosen, the justification for the approaches used and any amendments made over the course of the PhD. The researcher also took steps to increase response rates and utilised public involvement in the creation of the information booklet to ensure the information provided to patients was readable and patient friendly.

The researcher also utilised the valuable knowledge and insight held by the academic supervisors and SSG members to update and improve the interview schedules created in each study chapter, and to reflect on the recommendations made to determine their feasibility and discuss how they could be incorporated into practice. This allowed the researcher to gain feedback from individuals with clinical and practical experience within the NHS at multiple stages throughout the research process which strengthened the relevancy of the questions created in the interview schedules and helped to improve the practical applicability of the recommendations created.

## **7.7 Conclusions**

The findings of the thesis provide the first insight into the views and experiences of primary and secondary care prescribers, community pharmacy staff and patients parents or carers in relation to the use of unlicensed medicines specifically in Wales. Patients receiving unlicensed medicines in Wales may be faced with a challenging process in which they are

required to take on increased responsibilities to ensure they can access their medicine when needed. However, there are many issues that are out of the patients' control that have been seen to delay or disrupt patient care, such as healthcare professionals understanding and acceptability of the use of unlicensed medicines. These experiences resulted in patients having specific concerns around whether or not they would be able to access their medicine when needed and the development of individual strategies to ensure supply. As patients were not always supported when delays occurred, they have reported potentially unsafe practices such as using medicines past their expiry date, or syringing the medicine off the floor when dropped. In order to improve the patient experience when receiving an unlicensed medicine in Wales, there is a clear need for integrated and patient-centred care.

The overall limited understanding and awareness of how and when unlicensed medicines should be used reported by prescribers in study 3 was identified as a key factor seen to lead to prescription errors, and delays and disruption to patient care. The issues raised by participants within this thesis and within the existing literature could be reduced by increasing integrated and patient-centred care and ensuring healthcare professionals across care settings have access to the same clinical information and are provided with clear and consistent information in teaching or guidance documents to support the use of unlicensed medicines.

Overall, in order to improve the patient experience when receiving an unlicensed medicine, the healthcare professionals involved in their care should be adequately trained to understand how and when unlicensed medicines should be used and supported in this practice. Integrated care systems would help to provide a seamless transition between care settings and consistent patient information is needed to inform the patient their medicine is unlicensed without causing concern, while also acknowledging the differences in accessibility of unlicensed medicines in comparison to licensed medicines to reduce the chance of delays after discharge.

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## 9. Appendices

### Appendix 1. Search strategies for each database used in the systematic review

#### Scopus (586)

1. unlicensed W/2 drug (358 results)
  2. unlicensed W/2 medicine (136 results)
  3. unlicensed W/2 medication (54 results)
  4. unlicensed W/2 preparation (10 results)
  5. unlicensed W/2 formulation (15 results)
- Go into saved searches use toolbar to combine searches
6. #1 OR #2 OR #3 OR #4 OR #5 (507 results)
  7. {specials} AND drug (56 results)
  8. {specials} AND medicine (33 results)
  9. {specials} AND medication (6 results)
  - 10 {specials} AND preparation (19 results)
  11. {specials} AND formulation (14 results)
  12. #7 OR #8 OR #9 OR #10 OR #11 (88 results)
  13. 6 OR 12 (586)

#### OVID - EMBASE (599)

1. unlicensed adj2 drug (364)
2. unlicensed adj2 drugs (115)
3. unlicensed adj2 medicine (47)
4. unlicensed adj2 medicines (131)
5. unlicensed adj2 medication (30)
6. unlicensed adj2 medications (37)
7. unlicensed adj2 formulation (3)
8. unlicensed adj2 formulations (16)
9. unlicensed adj2 preparation (7)
10. unlicensed adj2 preparations (11)
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (593)
12. Specials adj2 drug (3)
13. specials adj2 drugs (0)
14. specials adj2 medicine (0)
15. specials adj2 medicines (10)
16. specials adj2 medication (0)
17. specials adj2 medications (1)
18. specials adj2 formulation (1)
19. specials adj2 formulations (0)
20. specials adj2 preparation (0)
21. specials adj2 preparations {0}
22. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 (15)
23. 11 OR 22 (599)

## **EMCARE (212)**

1. unlicensed adj2 drug (152)
2. unlicensed adj2 drugs (32)
3. unlicensed adj2 medicine (19)
4. unlicensed adj2 medicines (34)
5. unlicensed adj2 medication (15)
6. unlicensed adj2 medications (15)
7. unlicensed adj2 preparation (1)
8. unlicensed adj2 preparations (0)
9. unlicensed adj2 formulation (0)
10. unlicensed adj2 formulations (3)
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (209)
12. specials adj2 drug (1)
13. specials adj2 drugs (0)
14. specials adj2 medicine (0)
15. specials adj2 medicines (2)
16. specials adj2 medication (0)
17. specials adj2 medications (1)
18. specials adj2 preparation (0)
19. specials adj2 preparations (0)
20. specials adj2 formulation (0)
21. specials adj2 formulations (0)
22. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 (4)
23. 11 OR 22 (212)

## **Joanna Briggs Institute (0)**

1. unlicensed adj2 drug (0)
2. unlicensed adj2 drugs (0)
3. unlicensed adj2 medicine (0)
4. unlicensed adj2 medicines (0)
5. unlicensed adj2 medication (0)
6. unlicensed adj2 medications (0)
7. unlicensed adj2 preparation (0)
8. unlicensed adj2 preparations (0)
9. unlicensed adj2 formulation (0)
10. unlicensed adj2 formulations (0)
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (0)
12. specials adj2 drug (0)
13. specials adj2 drugs (0)
14. specials adj2 medicine (0)
15. specials adj2 medicines (0)
16. specials adj2 medication (0)
17. specials adj2 medications (0)
18. specials adj2 preparation (0)
19. specials adj2 preparations (0)
20. specials adj2 formulation (0)
21. specials adj2 formulations (0)
22. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 (0)
23. 11 OR 22 (0)

## **MEDLINE (242)**

1. unlicensed adj2 drug (71)
2. unlicensed adj2 drugs (74)
3. unlicensed adj2 medicine (25)
4. unlicensed adj2 medicines (58)
5. unlicensed adj2 medication (15)
6. unlicensed adj2 medications (19)
7. unlicensed adj2 preparation (4)
8. unlicensed adj2 preparations (6)
9. unlicensed adj2 formulation (3)
10. unlicensed adj2 formulations (8)
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 (240)
12. specials adj2 drug (0)
13. specials adj2 drugs (0)
14. specials adj2 medicine (0)
15. specials adj2 medicines (2)
16. specials adj2 medication (0)
17. specials adj2 medications (1)
18. specials adj2 preparation (0)
19. specials adj2 preparations (0)
20. specials adj2 formulation (0)
21. specials adj2 formulations (0)
22. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 (3)
23. 11 OR 22 (242)

## **WEB OF SCIENCE (299)**

1. unlicensed NEAR/2 drug (169 results)
  2. unlicensed NEAR/2 medicine (99 results)
  3. unlicensed NEAR/2 medication (37 results)
  4. unlicensed NEAR/2 preparation (10 results)
  5. unlicensed NEAR/2 formulation (8 results)
- Go into search history use toolbar to combine searches
6. #1 OR #2 OR #3 OR #4 OR #5 (297 results)
  7. "specials" NEAR/2 drug (0 results)
  8. "specials" NEAR/2 medicine (2 results)
  9. "specials" NEAR/2 medication (1 results)
  - 10 "specials" NEAR/2 preparation (0 results)
  11. "specials" NEAR/2 formulation (0 results)
  12. #7 OR #8 OR #9 OR #10 OR #11 ( results)
  13. 6 OR 12 (299)

## **CINAHL (186)**

1. unlicensed N2 drug (87)
2. unlicensed N2 medicine (65)

3. unlicensed N2 medication (33)
4. unlicensed N2 preparation (3)
5. unlicensed N2 formulation (6)
6. combine 1-5 with OR (182)
7. "specials" N2 drug (2)
8. "specials" N2 medicine (5)
9. "specials" N2 medication (1)
10. "specials" N2 preparation (0)
11. "specials" N2 formulation (0)
12. combine 7-11 with OR (8)
13. 6 OR 12 (186)



## Appendix 2. Completed example of modified data extraction form used in the systematic review

Modified Data Extraction form for Qualitative studies.

Reviewer: Alesha	Date: Nov 2020
Author: Mukattash et al	Year of publication: 2012
Journal: Eur J Clin Pharmacol	Record Number: 9

### Study Description

Title : Children’s views on unlicensed/off-label paediatric prescribing and paediatric clinical trials

Methods: Qualitative, focus groups

Phenomena of interest/ aspect of patient journey: Children views on unlicensed medicines used for children

Participants: 123 children

Data analysis: Thematic analysis

Authors conclusions: *This is the first study to explore the views of healthy children on unlicensed medicine use in children. Children were able to recognise potential risks associated with the unlicensed use of medicines and felt it is necessary to test and licence more medicines in children.*

	Barriers and enablers	Findings (Aspect of patient journey)	Illustration from publication (page numbers)
Recipients of care	Knowledge and skills		
	Attitudes		
	Experiences		
General public	Knowledge and skills	Children’s own definitions of what a licence means were sought by the modulator prior to giving a	Pg 143 “It is like a permit so you can sell something” (R37; boy aged 11).

	Barriers and enablers	Findings (Aspect of patient journey)	Illustration from publication (page numbers)
		<p>facevalue definition or presenting this definition in slides to children. Pupils were able to link licensing to medicine safety and to permission for the medicine to be prescribed.</p> <p>Having viewed the slide show, pupils were also able to relate licensing to testing of medicines in humans and to medicine efficacy and cost-effectiveness.</p>	<p>“It is that you can sell it because it is safe” (R61; girl aged 10).          “If it [the medicine] is too dangerous it is not going to be sold or maybe given a licence to sell it but only for certain areas” (S26; boy aged 14).</p> <p>“... if it is tested and proves it works” (T11; boy aged 15). “It has to be viable. I mean it could cost millions to get a tiny amount of it” (T7; boy aged 16).</p>
	Attitudes - safety	Some pupils viewed unlicensed use of medicines in children as unsafe and unethical and felt that it is necessary to test more medicines in children to improve the availability of licensed medicines for children.	<p>Potential for overdose (S02) “... If not tested it won’t be written on the box, the amount we use may be too strong” (female, 13 years old)          Increase side effects (S07) “... I think that it [an unlicensed medicine] would be strong for children and also aggressive, it surely will increase the side effects of the medicine and not help the child” (male, 13 years old)          Unethical (S08) “It [unlicensed medicine use] is not ethical. Children do not have developed bodies like adults, this will harm them” (male, 13 years old)          Negative effect on development (T10) “It will affect their development, they are not developed as adults” (female, 16 years old)          Hazardous (R08) “It is a bit dangerous to give medicines that are not tested, it’s like testing them for the first time” (female, 11 years old)</p>
	Safety continued	Others felt that the unlicensed use of medicines in children is preferable to enrolling children in clinical trials. The latter view was adopted particularly by children who were already taking medicines on a regular basis	<p>The only choice (S24a) “... there is no need to risk the child in tests [clinical trials] since it [an unlicensed medicine] has been tested on adults. It [an unlicensed medicine] may save his life if there was no other choice”(female, 13 years old)          Benefits outweigh the risk (S05) “The child can get better and not necessarily worse. Those [unlicensed] medicines might work and if you don’t give them to the children they may die” (male, 13 years old)</p>

	Barriers and enablers	Findings (Aspect of patient journey)	Illustration from publication (page numbers)
	Attitudes – of healthcare professionals	The majority of participants said that they trust that doctors/pharmacists know enough about medicines so that they can choose a suitable dose of medicine even when the medicine has not been tested in children before	A 13-year-old boy said, “They [doctors/ pharmacists] have had experience with drugs for so many years, so I would have confidence they will select a suitable dose” (S3).
	Attitudes – importance of awareness	<p>Felt parents should be informed and watch over children,</p> <p>Trust towards parents</p> <p>Children should be told - Most of the participants thought that the child himself/ herself should be told when unlicensed use of medicines takes place. Younger children, however, suggested a younger age for the child to be told; 10–11 year-old children suggested an age of 10 years, while children of 13–14 and of 15–16 years old suggested an age of 14 years old, for the child to be told. The reason for telling the child was to alert the child to potential side effects that they might experience.</p>	<p>“It could be dangerous if they give the child the wrong amount of medicines. In this case if the parents do not know [that a medicine is unlicensed], they will not watch the child closely” (R06; girl aged 10). “Parents should know when you give their child such medicines, if anything goes wrong it may be because of the medicine” (T26; boy aged 16).</p> <p>“Yes, they have to tell the parents. If they know that the medicine is not licensed they will have the opportunity to change it and not give it to the child” (R03).</p> <p>a 13-year-old boy said “... if my Mum and Dad think the drug is safe then I trust them” (S25).</p> <p>“If they know and feel something wrong after taking the medicine, they will know it’s because of the medicine and then can tell their parents...” (R03; boy aged 10).</p>
		Pupils who thought the child should not be told about the unlicensed use of medicine felt that it would be enough to tell the parents/guardians if such prescribing takes place since telling children might frighten them and cause them to refuse taking the medicine	. An 11-year-old boy said, “No. It may scare them. The children won’t take the medicine if it makes them think it will make them worse” (R07). Another 13-year-old girl said, “If you tell the children they may not take it. Telling the parents is enough” (S21).

	Barriers and enablers	Findings (Aspect of patient journey)	Illustration from publication (page numbers)
		<p>Even though most of the participants felt that telling the parent and the child should be mandatory when the unlicensed use of a medicine takes place, they felt that this may influence the way the parents administer or the child takes the medicine; they thought if parents lose confidence in the safety of the medicine they may stop, reduce or alter the dose they give to the child.</p>	<p>“They may give the child two tablets instead of three” (R07; boy aged 11)</p>
		<p>When asked if they would be willing to take part in a clinical trial to assist with the licensing of medicines for use in other children, more than half of the children indicated that they would.</p> <p>Younger pupils (10–11 years old) were more likely than older children to indicate their willingness to participate in clinical trials demonstrating a more altruistic perspective. Participants in the 13–14 and 15– 16 age groups expressed less willingness to participate and tended to realise that there may be risks associated with participation in clinical trials.</p>	<p>Yes [I would like to participate in a clinical trial] because we might be benefiting other children” (R30), and an 11-year-old boy said, “If it will help others, yes” (R49).</p> <p>“If it is the very first time, then no, but if they have had 90% success then yes” (S12; boy aged 14).</p>
	<p>Attitudes – illness ad participation in clinical trials</p>	<p>on further discussion many participants felt that children in general should take part in clinical trials only if they were seriously ill and the medicine may help.</p> <p>Pupils generally felt that children should not be involved in clinical trials if they were not seriously ill even if they were in hospital and the medicine may help. They felt that patients who are not seriously ill may recover without the need for taking part in a</p>	<p>“If the child is really sick, I think they should. Because it may make him better and give them more chances to live” (R14; girl aged 11). “The child may be dying anyway, so it may be worth trying” (T03; boy aged 15).</p> <p>No [they should not participate], because there may be another medicine which may help them” (R13; girl aged 11). “They may get better without taking medicines” (R 17; girl aged 10).</p>

	Barriers and enablers	Findings (Aspect of patient journey)	Illustration from publication (page numbers)
		<p>clinical trial. In addition, there was recognition that involving children who are not seriously ill in a clinical trial could put them at increased risk of adverse effects</p> <p>In addition, the general view (particularly among older children) was not in favour of testing medicines in healthy children since they felt that such children will not benefit directly from such testing. Furthermore, the understanding that there may be harmful effects caused by participation in clinical trials tended to increase with age</p> <p>Children felt medicines should not be tested in babies unless seriously ill</p>	<p>“No, because it [participation in clinical trial] might make them sick and there may be no cure for this sickness” (T22; girl aged 15). “A [healthy] child may think this is a good thing because he will be the first one to try that medicine, but then they really don’t know how bad that medicine would make them” (T21; boy aged 15).</p> <p>“Only if they can save their life” (T17; boy aged 15)</p>
	Experiences		

	Barriers and enablers	Findings (Aspect of patient journey)	Illustration from publication (page numbers)
Health system constraints	Accessibility		
	Financial resources		
	Educational system		
	Internal and external communication		
	Authority and accountability		

	Procurement or distribution systems		
Social and political restraints:	Contracts		
	Laws and regulations		
	Influential people		

# Appendix 3. Examples of completed quality appraisal checklists



Paper for appraisal and reference: **Record number 1. Notcutt 2013**

**Section A: Are the results of the study valid?**

1. Did the study address a clearly focused issue?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

**HINT:** A question can be 'focused' in terms of

- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

**Comments:** To identify the areas of daily function most affected by the introduction of Sativex, a cannabis-based medicine, and the impact on caregivers and people with multiple sclerosis (MS).

2. Was the cohort recruited in an acceptable way?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

**HINT:** Look for selection bias which might compromise the generalisability of the findings:

- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

**Comments:** Good size sample, UK prescribers acted as Gatekeepers (not sure what areas they came from)

Is it worth continuing?

3. Was the exposure accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments: All patients receiving sativex

4. Was the outcome accurately measured to minimise bias?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
  - has a reliable system been established for detecting all the cases (for measuring disease occurrence)
    - were the measurement methods similar in the different groups
    - were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments: Questionnaire so not actual measurements as such, but all methods the same for each participant.



5. (a) Have the authors identified all important confounding factors?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT:  
• list the ones you think might be important, and ones the author missed

Comments: - Exposure to the medicine (number of daily sprays)  
- Disease groups (MS or other)

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT:  
• look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments: - MS Groups results separated

6. (a) Was the follow up of subjects complete enough?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider  
• the good or bad effects should have had long enough to reveal themselves  
• the persons that are lost to follow-up may have different outcomes than those available for assessment  
• in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments: Patients were invited once they had received the medicine for the previous 16 weeks

Section B: What are the results?

7. What are the results of this study?

HINT: Consider

- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments: The response rate was 57%, with 124 questionnaires returned. The majority of respondents and their caregivers reported improvements across a range of daily functional activities, alongside a reduction in the use of concomitant anti-spasticity medication and in the use of other healthcare resources.

8. How precise are the results?

HINT:

- look for the range of the confidence intervals, if given

Comments: Questionnaire so confidence levels not provided

9. Do you believe the results?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- big effect is hard to ignore
  - can it be due to bias, chance or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments: Patient responses

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider whether
- a cohort study was the appropriate method to answer this question
  - the subjects covered in this study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - you can quantify the local benefits and harms

Comments: The age and gender distribution of the patients closely resembles that seen in more than 1500 patients who took part in the clinical trials programme for Sativex, and it therefore seems likely that they represent a similar population (MHRA Public Assessment Sativex Report, 2010).

11. Do the results of this study fit with other available evidence?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

Comments: Discussion references supporting findings from other studies (RCT's).

12. What are the implications of this study for practice?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
    - for certain questions, observational studies provide the only evidence
    - recommendations from observational studies are always stronger when supported by other evidence

Comments: The results also show that the use of Sativex may be associated with a reduction in the use of other healthcare resources, and adds to the evidence of meaningful efficacy from placebo-controlled, randomised, double-blind clinical studies.

Paper for appraisal and reference: Record number 8. Mukattash et al., 2012

Section A: Are the results valid?

1. Was there a clear statement of the aims of the research?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- what was the goal of the research
- why it was thought important
- its relevance

Comments: To explore the views and perspectives of children on the unlicensed/off-label use of medicines in children and on the participation of children in clinical trials.

2. Is a qualitative methodology appropriate?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- Is qualitative research the right methodology for addressing the research goal

Comments: To gain views of different age groups

Is it worth continuing?

3. Was the research design appropriate to address the aims of the research?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

Comments: Qualitative justified but doesn't say why focus groups in particular

4. Was the recruitment strategy appropriate to the aims of the research?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the researcher has explained how the participants were selected
- If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
  - If there are any discussions around recruitment (e.g. why some people chose not to take part)

Comments:

5. Was the data collected in a way that addressed the research issue?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the setting for the data collection was justified
- If it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
- If the researcher has justified the methods chosen
  - If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
    - If methods were modified during the study. If so, has the researcher explained how and why
    - If the form of data is clear (e.g. tape recordings, video material, notes etc.)
      - If the researcher has discussed saturation of data

Comments: Focus groups, different ages of children

6. Has the relationship between researcher and participants been adequately considered?

Yes	<input type="checkbox"/>
Can't Tell	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
- How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

Comments:

Section B: What are the results?

7. Have ethical issues been taken into consideration?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
  - If approval has been sought from the ethics committee

Comments: ethical approval gained, assent gained from children

8. Was the data analysis sufficiently rigorous?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If there is an in-depth description of the analysis process
- If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
  - To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

Comments: Thematic analysis was used

9. Is there a clear statement of findings?

Yes	<input checked="" type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider whether

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher's arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

Comments:



Section C: Will the results help locally?

10. How valuable is the research?

HINT: Consider

- If the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy, or relevant research-based literature)
- If they identify new areas where research is necessary
- If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used

Comments: Valuable - first study to show childrens views for review shows public concerns and trust balance

## **Appendix 4. Examples of coded transcript pages.**

It was decided that sections of interview transcripts would be presented to show the coding process, however a full transcript will not be provided to safeguard participants and reduce the chance of identification.

being used unlicensed and they're happy with it and they're aware of the cost implications

I: right

P: I mean we've had a few um, I mean we had some last year, uh with the flu vaccination and one, uh two of the surgeries I think, or it might even have been three of the surgeries, um picked the specials liquid for the anti-viral by *mistake*, instead of the licensed one, which was going to cost an absolute arm and a leg

I: oh I see,

P: I wasn't going to be able to get it straight away and we spoke to all of the surgeries and got them all changed to the licensed prep because it was just a total, (pause ) mix up \*laughs\* I know you're recording so I won't say the other word \*laughs\*

I: \*laughs\*

P: so yeah, if there's anything that would concern me about it, like that one, yeah we'll contact them, yeah just ring the surgery and say 'can I speak to the GP' and 'do you know what you've done?' 'do you know how much this is gonna cost?' 'do you know they can't have this straight away there's only one place in the country that even *makes* it \*laughs\*

I: \*laughs\*

P: it was just insane, so if I've got any concerns I'll contact them, but the majority of ours are regular, and um yeah, so we've, already had that conversation

I: right, so do you get prescriptions from hospitals as well?

P: um, trying to think, we sometimes get them for melatonin capsules, but um generally they've had them before and it's usually the specialist unit that does it so, if I've had the conversation with the carer or the patient and I'm happy that it's all gone through, then I wouldn't necessarily speak to the uh prescriber, I have done but, very rarely

I: ok and are there any clinical or professional checks in your SOP's that you undertake when you get a prescription for a special?



P: Um it's difficult, cause often when we get the prescriptions through secondary care it it's, sometimes it's not clear-explicitly said what the indication is, therefore it may not highlight that it's not that license application, so they've initiated, we will continue prescribing, but um I it would come up in medication reviews, but I can't think of any that really kind of stick out, um and I guess we wouldn't override it, you know, we just continue if if it was, even if it's unlicensed for that use, we would continue, cause it's normally because they've tried multiple other medications, prior to that, especially if it's come from secondary care.

I: Yeah, so with the prescriptions you get from secondary care in sort of general, then what sort of information do you get with those prescriptions? So do you get things like the reason for why those medicines have been selected?

P: (nods) um you get the indication normally, so um we don't get prescriptions, we get a copy of the prescriptions they're if they're actually issued from secondary care, so from the hospital pharmacy you would get a copy of the of the prescription, if the, only if the patient drops it in.

I: Right.

P: so and then the other so we don't actually get a physical copy of the prescription, unless the patient drops it in, which most of them do, um but um what we get is the letter from the secondary care clinic explaining you know the, the clinic encounter, what happened during the clinic and um and what the outcome was with them prescribing, so the prescriptions don't generally come via us, and then if they, um ask to continue prescribing, um generally, or they will ask us to start the medication

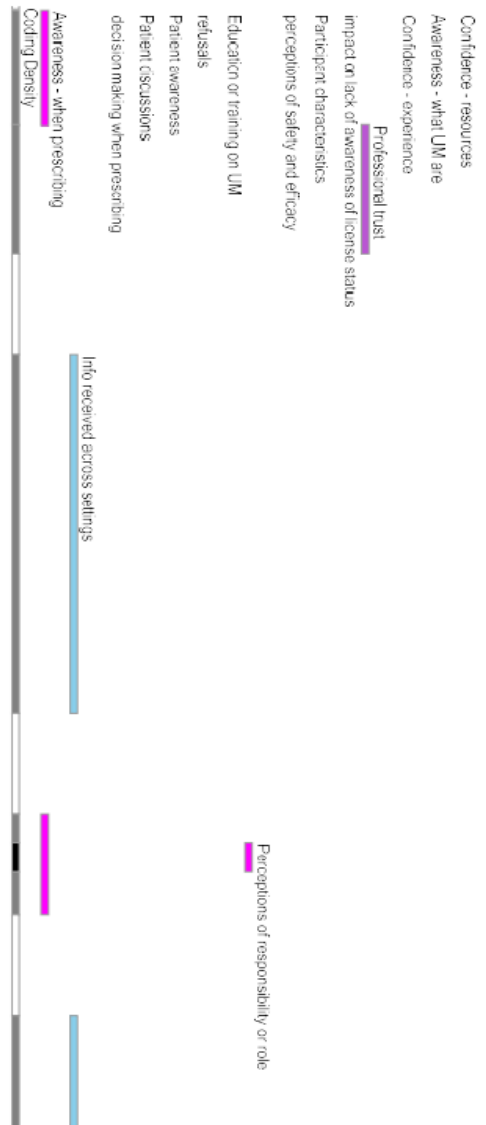
I: Ah oK.

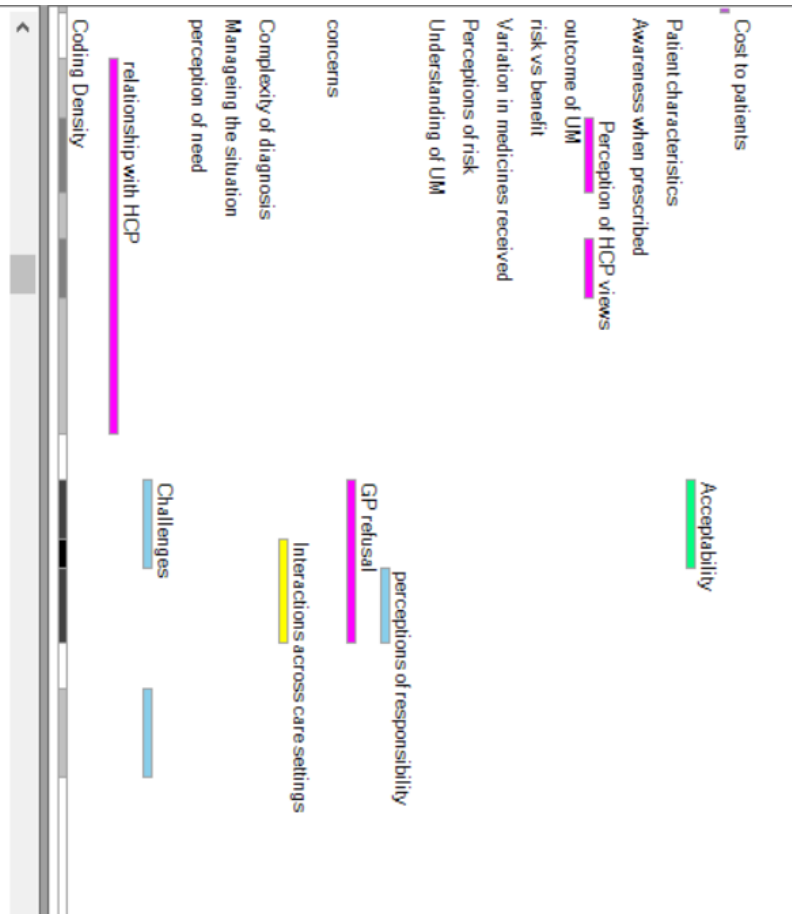
P: So either they will give the hospital prescription which is less often, especially if it's something that's used quite a lot or they'll write to us asking us to start prescribing it, um and I guess it, I don't think it happens that often, but I'd be, because it's not us making the clinical decision about starting the medication, I think we're often less aware of of the, sort of issues around it.

I: Yeah, so with the clinic letter then, so even if it doesn't exactly specify, it's an unlicensed medicine, it will still give you some information about why that medicine in particular is being used, even if it doesn't say, this is unlicensed.

P: yeah so and actually, I think probably it's less likely to say to explicitly state this is an unlicensed use.

I: OK,





I: OK

P: but like still, I should have been entitled to free, but my GP in Cardiff wouldn't write the script because it wasn't a license medication and because she didn't believe the private consultant's recommendation,

I: Right

P: Even though symptomatically, I was a lot improved, it was all about budgets and they didn't really care, so I got on a waiting list for endocrinology in heath hospital, and I was on a waiting list for about a year, maybe 14 months and I got into the heath hospital saw [redacted] in there and he just prescribed it, when I saw him, like no problem at all, and since then I've had it on the NHS

I: Fab

P: but it's been a struggle, because the GP every, for the first few years every six months when it would come up for renewal, the GP would say I'm not writing it, you go back to the Heath, and I go up to the hospital, and then they'd say like they'd write a stern letter to the GP and say, write it. I'm telling you to write it.

I: Ah right

P: So yeah, as a patient it was a very poor experience because I had to be going here to there quite a lot and there wastimes where I was just left short, um so I paid for privately so, it did get expensive. (pause) oh you froze again, sorry.

I: OK, I'll keep waving until



P: ah got you

## Appendix 5. Newsletters sent to the stakeholder steering group

# Unlicensed 'special' medicines

## *Steering Group Newsletter*

Alesha Wale, BSc, MSc.

1/10/2019



Dear steering group members, thank you for taking the time to read this newsletter. The newsletter contains an update on the progress of the project, a description of the steps taken during the ethical approval process and the next steps to be taken once approvals have been gained, along with details of the next steering group meeting.

### *Progress Update on Research Project*

In the last steering group meeting, identifying gatekeepers with access to potential participants was discussed, along with plausible recruitment methods for both study one and study two. Since this time, much has taken place. Figure 1. shows a timeline of the steps taken during this time up to the point of submission for ethical approval.



Figure 1. Steps taken before IRAS submission.

Since submission for ethical approval, in preparation for upcoming data collection, further interview training has been obtained.

An abstract related to the results from study one has been submitted for the Health Services Research & Pharmacy Practice Conference 2020.

The early stages of a systematic literature review are being conducted to explore the factors that affect the patient journey when receiving an unlicensed medicine.

### *The Ethical Approval Process*

An application for ethical approval was submitted to the NHS through the IRAS on the 23<sup>rd</sup> August 2019. This consisted of a 125-page application, containing the IRAS application, the project protocol, copies of all the supporting documents and copies of the interview schedules. The application was put forward for proportionate review at the North West - Liverpool Central Research Ethics Committee.

A favourable opinion was given with conditions on the 4<sup>th</sup> September 2019. Conditions included clarifying how gatekeepers would be identified

for each study, and how information would be stored and transferred throughout the research process.

While reviewing and addressing the comments made, contact was made with the Primary Care Research Manager and the Director of Support and Delivery for Health and Care Research Wales. They have agreed to act as a Gatekeeper and circulate the information, for study two, to GP surgeries who are part of the Primary Care Research Incentive Scheme (PICRIS) across Wales.

The conditions and comments received were addressed. The protocol and supporting documents were updated and uploaded to the IRAS on the 25<sup>th</sup> September 2019.

### *Next steps...*

Once formal approval has been gained, before recruitment, data collection and analysis can begin:

- Contact will be made with each health board to share information about the project.
- Selected community pharmacies will be updated of upcoming research.
- Patient information booklets will be ordered.

- Contact will be made with dermatology groups and gatekeepers for secondary care clinicians in each health board will be identified.
- The study advertisement will be placed on social media and HealthWise Wales.
- Study information will be sent to contacts at Health and Care Research Wales for circulation to the PICRIS group.

### *Upcoming Steering group meeting*

The next steering group meeting has been arranged for the 9<sup>th</sup> December 2019 at 2pm and will take place at Redwood building, King Edward VII Avenue, Cardiff, CF10 3NB. Those who will not be able to attend will be sent a summary of the discussions held.

If you would like any more information about the study, or the updates made prior to the next steering group meeting, please feel free to contact me at any point.

Alesha Wale –



Nysgol Iechyd a Sgiliau Economi Gwybodaeth  
Knowledge Economy Skills Scholarships



# Unlicensed 'special' medicines

## Steering Group Newsletter



Dear steering group members, thank you for taking the time to read this newsletter. The newsletter contains an update on the progress of the project, a description of the steps taken during the ongoing study set up across the seven health boards, and lastly some next steps for recruitment.

### *Progress Update on Research Project*

Since the last steering group meeting took place, HRA and HCRW approvals have been gained. Figure 1. shows a timeline of the steps taken since the last steering group meeting. Alesha attended and presented at a monthly dermatology meeting (11<sup>th</sup> March) to begin recruitment and access of potential Gatekeepers. As not all members were in attendance, one member volunteered to disseminate the

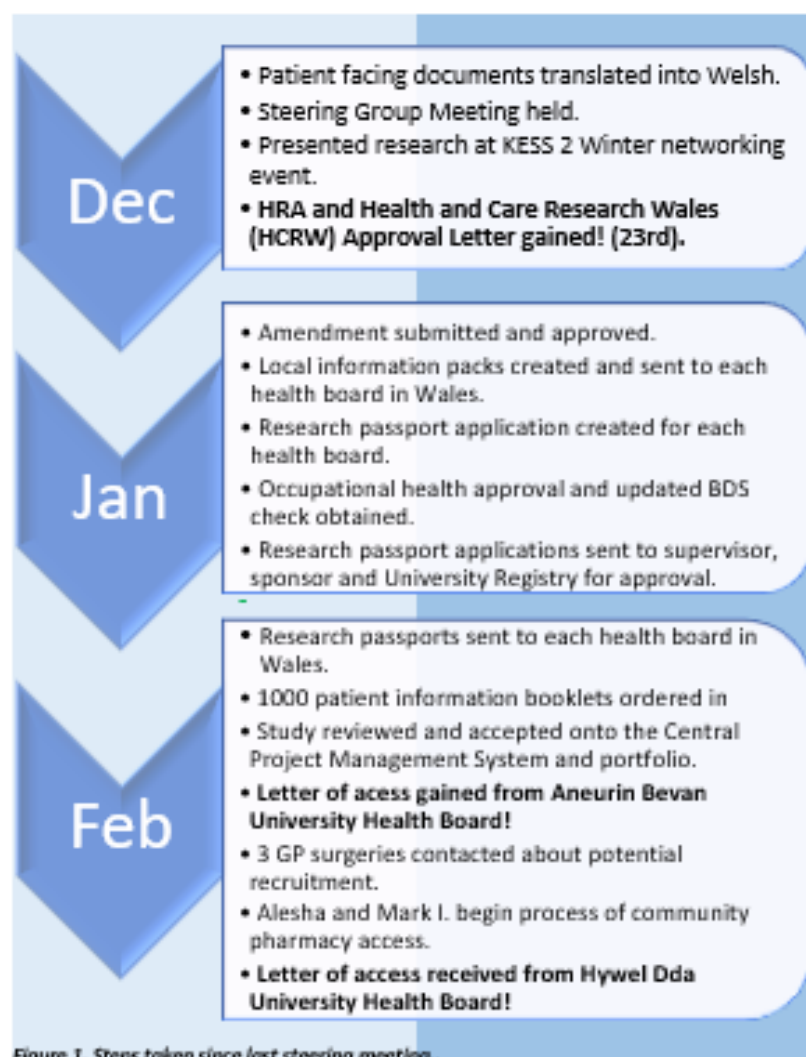


Figure 1. Steps taken since last steering meeting..



Information packs to the missing members.

[In an effort to](#) improve the methods and results of the planned systematic literature review, further training was sought and will take place in Oxford 16-18th March 2020.

Since full ethical approvals have been gained, the study information had been sent to each health board within Wales for individual approvals to be sought. As each health board has different methods of doing this, some variation in access received and timelines involved can be seen.

### *The everlasting Approval Process*

After NHS ethical approvals had been received, the local information packs were created and sent to each health board. Due to technical issues within the health boards that resulted in the documents being blocked, no information packs were received. This led to a slight delay having to send each health board each supporting document in individual emails. However, technical issues were still experienced. To combat this, an account was set up on the NHS online secure portal and the information pack and research passport applications



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Knowledge Economy Skills Scholarship

were sent to the health boards using this method. As part of the process, some health boards chose to assess the project for capacity prior to processing the research passport application pack. While others have suggested that capacity and passports will be approved and sent out at the same time. This has resulted in different stages of progress for approval within each health board, meaning recruitment will have to be staggered while awaiting the letter of access from other health boards.

### *Next Steps...*

Once all health boards have sent the letter of access, recruitment can proceed in remaining health boards.

- Contact will continue to be made with facilitators to obtain list of GP surgeries who were previously involved with [PICRIS](#) or are still research active.
- GP surgeries to continue to be contacted by Alesha directly.
- Mark Ireland and Alesha to continue to work together to set up studies in selected community pharmacies in Aneurin Bevan UHB, Hywel Dda UHB and remaining health boards once letter of access gained.
- Alesha to begin conducting interviews with GPs, [dermatologists](#) and patients.

- Health board facilitators to assist contact within Paediatric and Gastroenterology departments.
- The study advert will be sent to potential patient participants across the whole of Wales online through HealthWise Wales once access has been granted for all health boards.
- The abstract submitted for the HSRPP Conference 2020 has been accepted, a poster will be presented at the conference in April 2020.

### *Upcoming Steering group meeting*

The next steering group meeting will be arranged for June 2020 and will take place at Redwood building, King Edward VII Avenue, Cardiff, CF10 3NB. Those who will not be able to attend will be sent a summary of the discussions held.

If you would like any more information about the study, or the updates made prior to the next steering group meeting, please feel free to contact me at any point.

Alesha Wale –



# Unlicensed 'special' medicines Steering Group Newsletter



Dear steering group members, thank you for taking the time to read this newsletter. The newsletter contains an update on the progress of the project, and a description of the steps taken during the lockdown as a result of the COVID-19 global pandemic.

## *Progress Update on Research Project*

Since the last steering group meeting all recruitment has had to be postponed. Figure 1. shows a timeline of the steps taken since the last steering group meeting. Due to COVID-19, all non-essential research was postponed in the NHS meaning recruitment and data collection has also had to be postponed until further notice. Alesha and Efi have discussed a plan for moving the project forward, details will be outlined in the next page.



Figure 1. Steps taken since last steering meeting.

Once recruitment and data collection had been postponed, the focus was shifted from setting up the study within healthcare settings and contacting potential participants about recruitment, to experimental work that could be done remotely as well as a focus on writing and dissemination. Since research was postponed Alesha has finalised and submitted a journal article for review to the Integrated research and Pharmacy Practice Journal (many thanks to all steering group members for input or reviewing this). Alesha has also completed the systematic literature review protocol and has submitted this for registration on the PROSPERO website.

### Thesis Planning

Due to the Covid-19 pandemic, planning for the overall thesis has had to be adapted in many ways. KESS II have confirmed the option for a no-cost extension for the project and the research with the possibility of a funded extension. As such, the research plan has been extended for a further three months to reflect the delays experienced to date and allow further time for data collection and analysis to be completed.



Anticipated end date now: June 31<sup>st</sup> 2021.

Other adaptations include focussing on an experimental chapter consisting of a full systematic literature review, exploring the patient journey and patient care when receiving an unlicensed medicine in the UK.

It has also been understood by the University that due to the global pandemic, the sample sizes planned and anticipated may not be able to be met. With this in mind, the plan for recruitment once able to resume, has been edited slightly and is described below.

### Next Steps...

Once health boards have given approval for non-essential research to continue:

- Mark Ireland and Alesha to continue to work together to set up studies in selected community pharmacies in Aneurin Bevan UHB, Hywel Dda UHB, Powys Teaching UHB once health boards have granted access again.
- Contact will continue to be made with facilitators to obtain list of GP surgeries who were previously involved with PiCBIS or are still research active and contacted by Alesha about involvement.

- Health board facilitators to assist contact within secondary care dermatology, paediatrics and gastroenterology departments.
- Alesha to begin conducting interviews with secondary care clinicians and patients when possible.
- Alesha plans to present research at the three-minute thesis competition at Cardiff University Doctoral academy.

### Upcoming Steering group meeting

The next steering group meeting will plan to be arranged for September 2020 and will take place virtually. Further updates and confirmation of meeting details will be provided nearer the time, depending on availability.

If you would like any more information about the study, or the updates made prior to the next steering group meeting, please feel free to contact me at any point.

Alesha Wale –



# Unlicensed 'special' medicines Steering Group Newsletter



Dear steering group members, thank you for taking the time to read this newsletter. The newsletter contains an update on the progress of the project, and a description of the steps taken over the last few months.

### *Progress Update on Research Project*

Since the last update, efforts have continued to be focussed on the systematic review and writing towards the overall PhD thesis. Recently, some Health Boards have allowed the study to be restarted and so study set up and recruitment has begun in some areas. Figure 1. Shows the steps taken while awaiting study restart and the beginning steps of recruitment in some areas. Not all health boards have approved study re-start and so the recruitment plan has had to be altered slightly.



Figure 1. Steps taken

We are working to get the study approved for re-start across health boards however, the current pandemic is still having an impact on recruitment, with some sites saying they are still too busy to support the research at this time.

One health board has asked for additional requirements and so an amendment to address this was submitted and approved on (02/09/2020).

The systematic review protocol submitted to PROSPERO has been accepted given the registration number CRD42020190201 and can be accessed on the PROSPERO website.

### Thesis Planning

Due to the Covid-19 pandemic, planning for the overall thesis has had to be adapted in many ways.

KESS II have now announced the potential for a funded 6-month extension for research projects that have been significantly impacted. We have applied for this and are awaiting confirmation to be received on the [9<sup>th</sup>](#) November.

As such, the research plan has been extended by six months to reflect the delays experienced to date, and allow further time for study set up, data collection and analysis to be completed.



Anticipated end date now: September 31<sup>st</sup> [2021](#)

Alesha has continued to write towards the overall thesis, introduction, and methodology chapters, gaining feedback from supervisors.

Abstracts collected for the systematic review have been reviewed and screened for inclusion.

Preparations have been made to ensure all participant interviews can be conducted virtually.

Further contact has been made with GP sites and community pharmacies and more patient information booklets have been sent out.

### Next Steps...

As health board approvals for re-start continue to be gained:

- Rhodri Thomas and Alesha to continue to work together to set up studies in selected community pharmacies.
- Contact will continue to be made with facilitators to obtain list of GP surgeries who were previously involved with ~~PiCRIS~~ or are still research active and contacted by Alesha about involvement.
- Alesha to continue contact with Health Boards to discuss when set up and recruitment can begin in secondary care settings.

- Recruitment to be continued where possible and data collection of GPs and patients to begin.
- Full papers of selected abstracts to be screened for inclusion in full systematic review.
- Selected papers to be reviewed and synthesised using narrative synthesis.
- Write up of systematic review to begin.

### Upcoming Steering group meeting

The next steering group meeting will plan to be arranged for December 2020 and will take place virtually. Further updates and confirmation of meeting details will be provided nearer the time, depending on availability.

If you would like any more information about the study, or the updates made prior to the next steering group meeting, please feel free to contact me at any point.

Alesha Wale –



# Unlicensed 'special' medicines

## Steering Group Newsletter

CARDIFF  
UNIVERSITY

PRIFYSGOL  
CAERDYDD

Alesha Wale, BSc, MSc.

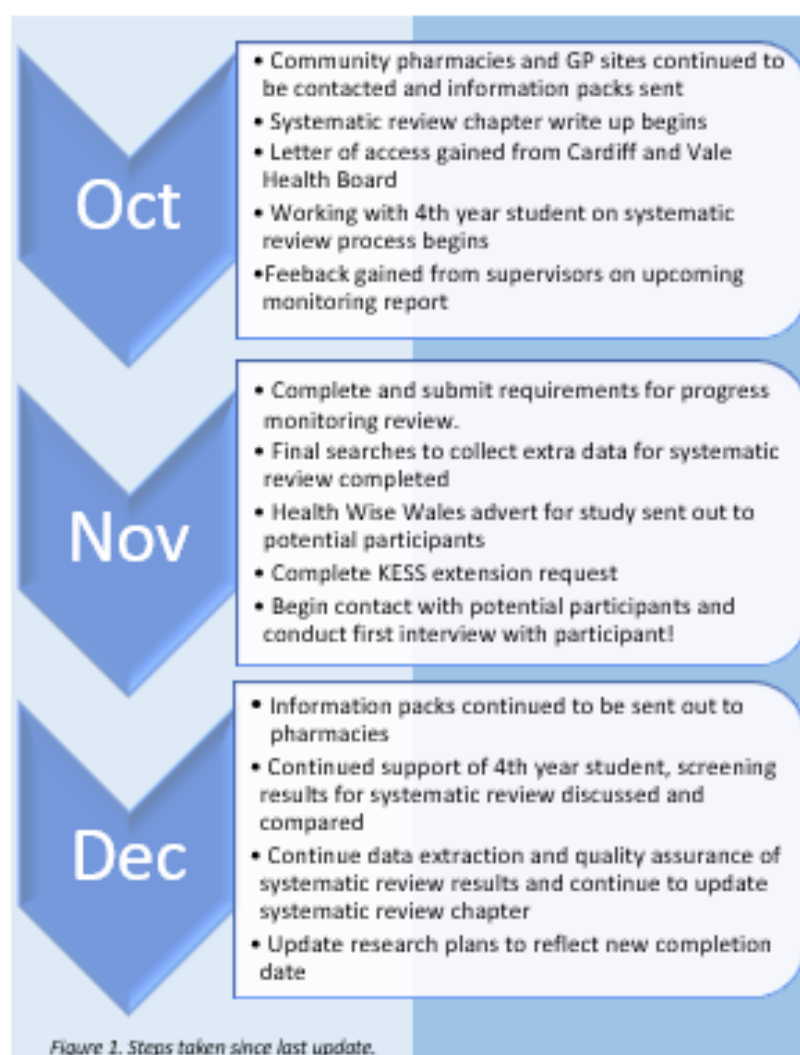
15/01/2021



Dear steering group members, thank you for taking the time to read this newsletter. The newsletter contains an update on the progress of the project, and a description of the steps taken over the last few months.

### *Progress Update on Research Project*

Since the last update, recruitment and data collection has begun. Health board approvals and recruitment within community pharmacies has been focussed on, while secondary care settings continue to be extremely busy dealing with the ongoing pressures caused as a result of COVID-19. In order to recruit patients, the study was also advertised by Health Wise Wales. Figure one outlines some of the key steps taken over the last few months and the progress made.



Five of the 7 health boards have now given approvals for the study to be restarted and another health board has recently updated their [OJD](#) so we are expecting to gain another approval there soon.

Recruitment began by first contacting community pharmacy sites and sending out information packs for potential participants, GP sites have also been contacted and sent information too, and this continues to be an ongoing process.

Due to the delays experienced, we had applied for an extension to the project and have been granted a [4.5 month](#) extension bringing the anticipated end date to Aug 16<sup>th</sup> 2021.

[In order to](#) ensure recruitment can continue, Alesha has submitted an amendment through the IRAS to extend the project and recruitment dates. This has been approved and sent out to all health boards.

### *Progress with recruitment and thesis...*

Another 2 participants (1 prescriber and 1 patient) have been interviewed in January. The study information has begun to be disseminated in some secondary care departments (depending on approval from the health board and selected Gatekeepers).



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Alesha has continued to write towards the overall thesis, introduction, and systematic review chapters, gaining feedback from supervisors.

Alesha has also helped to oversee a fourth-year student conducting a rapid review on the topic of Unlicensed medicines and has therefore gained a second reviewer to help validate the deduplication and screening processes taken during the systematic review.

As part of the University's monitoring process, the systematic review chapter with preliminary results was submitted and a progress Viva to discuss the report and progress was held.

### *Next Steps...*

[In order to](#) continue recruitment:

- Rhodri Thomas and Alesha to continue to work together to set up studies in selected community pharmacies.
- Contact will continue to be made with GP sites to determine capacity and continue to try and set up recruitment of prescribers.
- Alesha to continue contact with secondary care departments about potential set up for the recruitment of prescribers and patients.
- Recruitment and data collection to be continued where possible.

For thesis:

- Alesha will continue writing towards thesis chapters and gaining feedback from supervisors.
- Selected papers for systematic review to be reviewed and synthesised using narrative synthesis.
- Write up of systematic review to be completed.
- Alesha will also look to write up the systematic review results in an acceptable format for publication. (Steering group members will be updated as this progresses).

### *Contact information*

Alesha will continue to update the steering group through newsletters for the time being as it is understood that many of the members are healthcare professionals and may continue to be extremely busy.

If you would like any more information about the study, or the updates made prior to the next steering group newsletter, please feel free to contact me at any point.

Alesha Wale –



# Unlicensed 'special' medicines Steering Group Newsletter



Dear steering group members, thank you for taking the time to read this newsletter. The newsletter contains an update on the progress of the project, a description of the steps taken over the last few months, and an outline of work to be undertaken in the future.

### *Progress Update on Research Project*

Since the last update, recruitment and data collection has continued. We are very close to the end of the recruitment period and Alesha has been focussing on analysing the results gained and writing towards the full thesis.

Figure 1. outlines some of the progress and actions taken over the last few months.



Figure 1. Progress and actions taken since last update.



Since the last update, Alesha has completed an abstract, lay summary and short presentation for the postgraduate research day. The initial results gained from prescribers and patients were presented and discussed at a collaboration meeting at St Mary's Pharmaceutical Unit.

### *Updates on recruitment numbers*

To date, a total of 15 participants have taken part in and completed an interview, this consists of:

- 6 community pharmacy staff members
- 5 prescribers
- 4 patients

One patient completed the survey card in the patient information booklet but expressed that they did not want to take part in an interview. Recruitment is planned to end 30<sup>th</sup> June 2021.

### *Updates on thesis write up*

Alesha has been working on writing up chapters towards the overall thesis using feedback from Efi and Rowan (the academic supervisors). As the project was extended, the final submission deadline is due in Feb 2022, however Alesha will aim to complete the first full draft of the thesis in October 2021.



The systematic review exploring the factors affecting the patient journey and patient care when receiving an unlicensed medicine in the UK has been completed and the write up of the full chapter and results are underway.

At the end of this newsletter an infographic containing some of the **key findings of the systematic review**, along with some potential discussion points will be provided. These results will be discussed in the next steering group meeting along with the **final results of all interviews conducted**. If you have **any feedback on the infographic** that you would like to share before then, please get in touch. Any feedback would be appreciated.

### *Next steps for write up and thesis completion*

- Alesha will continue writing towards thesis chapters and gaining feedback from supervisors.
- Alesha to finalise analysis of all interviews conducted and finalise write up of results.
- Alesha will also look to write up the systematic review results in an acceptable format for publication. (Steering group members will be updated as this progresses).

### *Triangulation*

- A steering group meeting for triangulation of the results is needed for the PhD which will take place in October (depending on steering group members' availability)
- All results will be presented and discussed with the aim of triangulating the findings and creating suggestions for improvements and next steps.
- Discussions had at this meeting will be written up into a triangulation chapter within the thesis.

### *Contact information*

If you have any questions or would like to discuss anything please feel free to get in touch

Alesha Wale –



## Factors affecting the patient journey and patient care when receiving an unlicensed medicine in the UK: A systematic review

**Aim:** To get a better understanding of the patient journey and patient care when receiving an unlicensed medicine in the UK, and to identify the factors that can affect it.

**Databases used:** Scopus; OVID; EMCARE; EMBASE; OVID Medline (R) ALL; CINAHL (The Cumulative Index to Nursing and Allied Health Literature); Web of Science; Joanna Briggs Institute (JBI).

**Analysis:** A total of 45 studies were included in the narrative synthesis. **Figure 1.** shows the themes and sub-themes identified. **Figure 2.** shows factors that were highlighted to impact different areas of the supply chain when a patient requires unlicensed medicines.



Figure 1. Themes and sub-themes identified

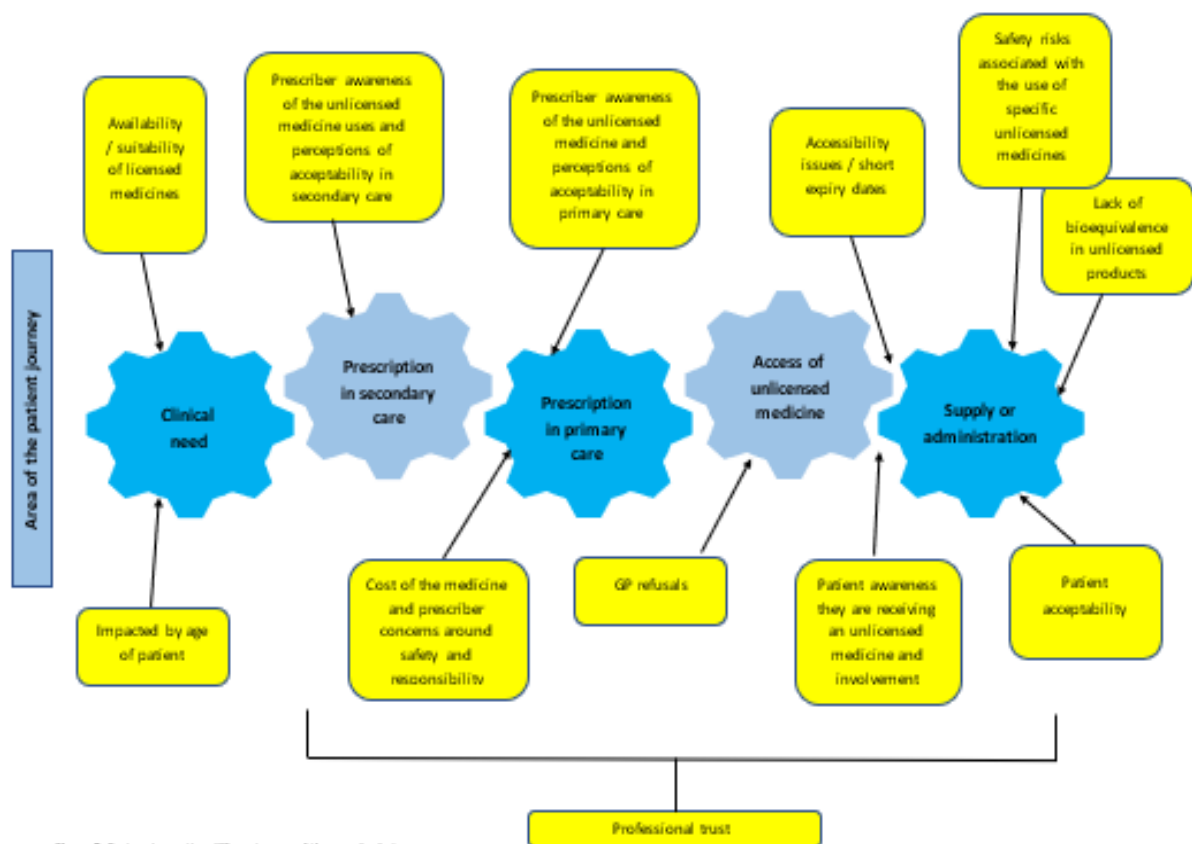


Figure 2. Factors impacting different areas of the supply chain

### Discussion points

- Professional trust is vital in ensuring the successful use of unlicensed medicines across the supply chain. The professional trust described highlighted a hierarchy of staff with prescribers in secondary care trusting the guidance issued by authorities such as NICE or the [BMJ](#). Primary care prescribers, trusting the knowledge and expertise of secondary care prescribers, and community pharmacy staff and nurses trusting prescribers across settings, although this trust was found in some cases to lead to a reluctance to question prescribers' decision.
- Community pharmacy staff also place professional trust on the suppliers and manufacturers of unlicensed medicines and the [patients](#) and the public have trust in healthcare professionals. However, some members of the public reported that they would refuse an unlicensed treatment having possible implications on adherence.
- The awareness of the use of unlicensed medicines was seen to impact prescribing behaviours with secondary care specialist prescribers prescribing unlicensed and off-label medicines more confidently than primary care prescribers, however even in the specialist group the use of an unlicensed medicine that was known to be dangerous in pregnancy was used due to a lack of awareness about specific indications, having implications for patient safety.
- Perceptions of acceptability were also seen to impact prescribing with GPs describing specific concerns around the use of unlicensed medicines and their legal responsibilities leading to delays which then impacted the community staff ability to access and supply the medicines. GPs reported multiple factors that impacted their decision to prescribe, such as their own knowledge and the information received from secondary care however, there were inconsistent reports about [whether pt cost](#) was a factor that impacted prescribing behaviours.
- When looking at the supply of unlicensed medicines and patient care, issues were found with multiple formulations being available which were found to lead to inconsistent treatment across care settings. Different unlicensed formulations were found not to be bioequivalent to each other or when compared to the licensed alternatives, having implications for patient care.

## **Appendix 6. Study documentation**

### **Study 1 Supporting documents.**

Email invite for Gatekeeper

Email invite for participants

Participant information sheet

Participant consent form

Pharmacist interview schedule

Pharmacy technician interview schedule

Dear Mr XXX

Re: Unlicensed 'Special' medicines; improving the patients' experience.

We are writing to invite you to participate in our study!

Please find attached an email invitation, information sheet and consent form. As agreed, these are to be forwarded by email to every pharmacist and pharmacy technician currently working for Mayberry pharmacy with a minimum of 1 year experience working in a community pharmacy setting. Please resend these documents as a reminder after two weeks of the original send date as discussed.

If you have any questions or wish to discuss anything about the study, please contact the research team.

We look forward to hearing from you,

Kind Regards,

Alesha Wale, BSc, MSc.

Dr Efi Mantzourani  
Cardiff School of Pharmacy and  
Pharmaceutical Sciences  
Email: [EMAIL ADDRESS]  
Tel: 029-2087 0452

Miss Alesha Wale, BSc, MSc.  
Cardiff School of Pharmacy and  
Pharmaceutical Sciences  
E-mail: [EMAIL ADDRESS]

Dear Sir/Ms,

Subject: For the attention of Pharmacists and pharmacy technicians.

Re: Unlicensed 'Special' medicines; improving the patients' experience.

My name is Alesha Wale, I am currently working on a research project as part of an MPhil with the University of Cardiff. The project aims to look at the use of unlicensed medicines in community pharmacies.

We are emailing you to invite you to participate in our study. Participation is voluntary and will involve taking part in an interview lasting approx. 20-30 mins at a time of your convenience. Attached is a participant information sheet for reference. If you would like to be involved, please contact the researcher directly or you can give permission for Mr Jon Smith to pass your details on to us and we will be in touch.

If you have any questions or wish to discuss anything about the study, please contact the research team.

We look forward to hearing from you,

Kind regards,

Alesha Wale, BSc, MSc.

Dr Efi Mantzourani

Cardiff School of Pharmacy and  
Pharmaceutical Sciences

Email: [EMAIL ADDRESS]

Tel: 029-2087 0452

Miss Alesha Wale, BSc, MSc.

Cardiff School of Pharmacy and  
Pharmaceutical Sciences

E-mail: [EMAIL ADDRESS]





## Participant information sheet

### Project Title: Unlicensed 'special' medicines; Improving the patients' experience

We would like to invite you to take part in our study. Before you decide if you would like to take part we would like you to understand why the study is being undertaken and what it would involve for you.

#### Introduction

Unlicensed 'special' medicines are used when no other licensed medication is available and are often made to treat a specific individual. This can make obtaining them quite difficult and means they are not subjected to the same the level of quality control testing as licensed medicines. Although there are laws and regulations around the use of unlicensed medicines in the UK, there is little evidence available on the experiences and perceptions of the pharmacists and pharmacy technicians who procure and dispense these medicines.

#### What is the purpose of the study?

This study aims to get your views on strengths and weaknesses in the process, and provide suggestions for improving your experiences.

#### Why have I been invited to participate?

You have been invited because you are a registered pharmacist or pharmacy technician working at a Mayberry Community Pharmacy and have been involved in procuring and dispensing unlicensed medicines.

#### Do I have to take part?

You are under no obligation to take part in the study; participation is voluntary.

#### What do I have to do?

There will be opportunity to ask questions to the research team about the study via e-mail before confirming to take part or not. If you agree to take part, please email the researcher, Miss Alesha Wale, directly to arrange a time to come to the pharmacy and conduct the interview at your convenience. Before the interview the researcher will ask you to sign a consent form. Following consent the researcher will start the interview. The interview will last around 20-30 minutes and will be conducted face-to-face in a suitable area of the pharmacy you work in (or by telephone if required). The interview will be recorded with a Dictaphone, transcribed verbatim and then analysed following the interview. The audio tapes will be deleted after transcription.

#### What happens next?

The researcher will look for recurring topics and devise recommendations based on those topics. The study will be written up to complete a thesis for the MPhil with Cardiff University and results may be published in national and international conferences and journals. A report of the findings and any suggestions for improvement will be disseminated to St Mary's Pharmaceutical Unit (SMPU) and Mayberry pharmacy.

**Will my participation in the study be kept confidential?**

Yes, the information provided will be kept strictly confidential by the researcher, all recordings will be destroyed and data will be anonymised in the final report. Consent forms will be stored securely for 1 year in accordance with the Data Protection Act 2018, with no way of connecting consent forms to individual comments, and then destroyed.

**What happens if I don't want to take part/carry on with the study?**

You are free to withdraw at any time, without giving a reason. This will not affect you in any way. If you withdraw before complete data anonymity has been reached, the data collected from the interview will be destroyed and will not be analysed in the report.

**Who has reviewed the study?**

The Cardiff University School of Pharmacy and Pharmaceutical Sciences Ethics Committee have reviewed this study.

**How to contact us**

If there is anything that is not clear, or if you would like more information, please contact the project supervisor, Dr Efi Mantzourani, or Miss Alesha Wale.

Dr Efi Mantzourani  
Cardiff School of Pharmacy and  
Pharmaceutical Sciences  
Email: [EMAIL ADDRESS]  
Tel: 029-2087 0452

Miss Alesha Wale, BSc, MSc.  
Cardiff School of Pharmacy and  
Pharmaceutical Sciences  
E-mail: [EMAIL ADDRESS]

**What if there is a problem?**

If you have any concerns or complaints during the course of this research project, please contact Dr Efi Mantzourani who will address the issue. If you remain unhappy and wish to complain formally, you can do this by contacting Professor Andrew Westwell, Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, [EMAIL ADDRESS].

*Thank you very much for taking the time to read this information sheet.*



### Consent Form

#### Unlicensed 'special' medicines; improving the patients' experience

	Please Initial box to consent
I confirm that I have read and understood the participation information sheet dated July 2018 (Version 1) provided for this study.	
I am aware that this is a voluntary study and I may withdraw at any time, without giving reason and this will not affect my legal rights in any way.	
I have been given opportunity to ask questions and these have been answered and explained to me.	
I understand that the information collected may be used to support other research and may be shared anonymously with other researchers.	
I agree to the interview being audio recorded.	
I agree to the use of anonymised quotes in publications.	
I understand that the information collected will remain confidential and that any identifiers will be removed from any information used during the write up process.	
I agree to take part in the above study	

Name of participant:

Name of researcher:

Date:

Date:

Signature:

Signature:



## Pharmacist interview schedule

Hello, thank you for taking the time to speak with me, before we begin I thought I'd just give you an overview of what we'll be talking about today. I'll start with asking a few general questions, then I'll ask about the processes involved in dealing with unlicensed medicines and lastly, I'll move on to asking about some of the experiences you have had. I just want to confirm that you've read the information sheet and signed the consent form? Do you have any questions before we begin?

Question	Notes
<p><b>'Setting the scene'</b></p> <p><i>May I start by asking about your age?</i></p> <p><i>How long have you been a registered pharmacist working in a community pharmacy?</i></p> <p><i>Do you have experience a different pharmacy sector?</i></p> <p><i>And can you tell me how you would define an unlicensed 'special' medicine?</i></p> <p><i>Can you tell me about how many specials are dispensed per month on average at this location?</i></p> <p><i>How do you feel about your role of responsibility in supplying unlicensed medicines to the public?</i></p>	
<p><b>Q1. Can you tell me a little about the process you go through when you first receive a prescription for an unlicensed medicine?</b></p> <p><i>Prompt: Tell me about that</i></p> <p><i>Can you tell me about the ways you receive prescriptions?</i></p> <p><i>Can you tell me about any contact you may have with the prescriber?</i></p> <p><i>Are there any additional clinical or professional checks in your SOPs that you undertake when you are presented with a specials prescription?</i></p> <p><i>Can you tell me a little about how you deal with potential amendments to the prescription if needed?</i></p>	
<p><b>Q2. After you have decided to dispense a special, this then needs to be ordered, in</b></p>	

<p><b>your pharmacy who has the main responsibility of ordering?</b></p> <p><i>Prompt: can you tell me about the processes you go through when ordering unlicensed medicines?</i></p> <p><i>Can you tell me a little about the different suppliers?</i></p> <p><i>Can you tell me about how you would choose a supplier? Tell me about that.</i></p> <p><i>Can you tell me about timelines involved in ordering specials?</i></p> <p><i>Have you ever had to have an unlicensed medicine imported? Tell me about that.</i></p>	
<p><b>Q3. Once you have received the product from the supplier can you tell me a little about how you supply the medication to the patient</b></p> <p><i>Prompt: Tell me about that,</i></p> <p><i>Have you ever needed to make a Product Specification sheet? Tell me about that</i></p> <p><i>Can you tell me about how you support patients who use specials?</i></p> <p><i>How do you use the information supplied by the drug tariff?</i></p> <p><i>Tell me about timelines in supplying specials, any delays?</i></p> <p><i>How do you use any guidelines or SOPs available for accessing and dispensing specials to support you? Tell me about that</i></p>	
<p><b>Q4. Can you tell me about your experience dealing with issues around the safety and efficacy of specials?</b></p> <p><i>Prompt: How do you feel about the safety and efficacy of medicines from different suppliers? Imported? Could you give me an example?</i></p>	

<p><i>How do you feel about the safety and efficacy of a specials with either a certificate of analysis or certificate of conformity?</i></p> <p><i>Can you tell me how you feel about the safety and efficacy of unlicensed medicines for use in different age groups?</i></p> <p><i>Have you ever had a situation where a patient has suffered due to treatment disruption of a special? Tell me about that.</i></p> <p><i>Have you ever had to report an ADR for an unlicensed medicine? Tell me about that.</i></p>	
<p><b>Q5. Overall, how do you feel about the impact of dealing with specials on your workflow?</b></p> <p><i>Prompt: Does it impact your timelines? Is this different for Licensed vs unlicensed?</i></p> <p><i>Can you tell me about how you get reimbursed for specials? Timelines?</i></p> <p><i>Does the process of reimbursement impact your workflow?</i></p> <p><i>Is there an Impact on you personally?</i></p>	
<p><b>Q6. Is there anything you would like to see change that you think could improve the process?</b></p> <p><i>Prompt: Are there any important issues that you think could be targeted to improve the process further?</i></p> <p><i>Is there anything you would like to add?</i></p> <p><i>Do you have any questions?</i></p>	

Thank you very much for taking the time to meet with me today and discuss your experiences!

**Pharmacy Technician interview schedule**

Hello, thank you for taking the time to speak with me, before we begin I thought I'd just give you an overview of what we'll be talking about today. I'll start with asking a few general questions, then I'll ask about the processes involved in dealing with unlicensed medicines and lastly, I'll move on to asking about some of the experiences you have had. I just want to

confirm that you've read the information sheet and signed the consent form? Do you have any questions before we begin?

Question	Notes
<p><b>'Setting the scene'</b></p> <p>May I start by asking how old you are?</p> <p>How long have you been a registered pharmacy technician working in a community pharmacy?</p> <p>Do you have experience a different pharmacy sector?</p> <p>And can you tell me how you would define an unlicensed 'special' medicine?</p> <p><i>How do you feel about your role of responsibility in supplying unlicensed medicines to the public?</i></p>	
<p><b>Q1. Can you tell me a little about the level of involvement you have when a prescription for an unlicensed medicine is first received?</b></p> <p><i>Prompt: Tell me about that</i></p> <p><i>Can you tell me about the ways you receive prescriptions?</i></p> <p><i>Can you tell me about any contact you may have with the prescriber?</i></p> <p><i>Are there any additional clinical or professional checks that you undertake when you are presented with a specials prescription?</i></p> <p><i>Can you tell me a little about how you deal with potential amendments to the prescription if needed?</i></p>	
<p><b>Q2. After the pharmacist has decided to dispense a special, in your pharmacy who has the main responsibility for ordering?</b></p> <p><i>Prompt: can you tell me about the processes you go through when ordering unlicensed medicines?</i></p>	

<p><i>Can you tell me a little about the different suppliers?</i></p> <p><i>Can you tell me about how you would choose a supplier? Tell me about that.</i></p> <p><i>Can you tell me about timelines involved in ordering specials?</i></p> <p><i>Have you ever had to have an unlicensed medicine imported? Tell me about that.</i></p>	
<p><b>Q3. Overall, how do you feel about the impact of dealing with specials on your workflow?</b></p> <p><i>Prompt: Does it impact your timelines? Is this different for Licensed vs unlicensed?</i></p> <p><i>Can you tell me about how you get reimbursed for specials? Timelines?</i></p> <p><i>Does the process of reimbursement impact your workflow?</i></p>	
<p><b>Q4. To conclude..... Is there anything you would like to see change that you think could improve the process?</b></p> <p><i>Prompt: Are there any important issues that you think could be targeted to improve the process further?</i></p> <p><i>Is there anything you would like to add?</i></p> <p><i>Do you have any questions?</i></p>	

Thank you very much for taking the time to meet with me today and discuss your experiences!

**Study 2 Supporting documents.**

HealthWise Wales/ Social media advert.

Cover letter for Gatekeepers in Primary care.

Cover letter for Gatekeepers in Secondary care.

Participant Information Booklet

Participant Information Sheet

Consent Form.

Interview Schedule.



## Research into unlicensed medicines

**Are you, or someone you care for, using unlicensed ‘special’ medicines? Would you consider spending 10-20 minutes of your time to help improve the care and support you receive?**

Many patients need an unlicensed ‘special’ medicine to treat their condition. Unlike licensed medicines, unlicensed ‘special’ medicines can sometimes be harder to access and riskier to take. There is little known about the views and experiences of the patients who receive unlicensed ‘special’ medicines in Wales, or of the processes they use to do this.

In Cardiff University, we are conducting a study to explore the views and experiences of patients who receive unlicensed ‘special’ medicines. The study will involve completing a small survey and taking part in a short interview. Interviews are expected to last between 10-20 minutes and will be held at a time and location of convenience to the participant. Anyone who participates in the interview will receive a **£15 high street voucher**.

If you would like more information, or to find out if you are eligible and would like to take part in this study, please contact Miss Alesha Wale at [EMAIL ADDRESS] or on 07564247000.



Dear [insert name here],

[ Date ]

We have identified this pharmacy as one of the highest dispensing pharmacies for unlicensed 'special' medicines in Wales. We would like to invite you to act as a gatekeeper in our research regarding the use of unlicensed medicines.

If your pharmacy dispenses most of its unlicensed medicines directly to care homes, it may not be suitable for this project. However, if unlicensed medicines are usually dispensed on an individual basis where patients or their carers will come to the pharmacy to collect them, then please keep reading.

As a gatekeeper we would like you to identify when unlicensed 'special' medicines are being dispensed from your pharmacy and supply the patients or carers collecting the dispensed prescription with our information booklets and prepaid envelopes, and explain that they are invited to participate in a study run by Cardiff University, looking at improving their experiences with their medicines. To help you do this, we have provided stickers which can be put on patients' medicine bags which will remind you, or a member of your team, to supply the patient with a copy of the booklet and a prepaid envelope upon collection. All the information is included in the booklets. If you are asked for any further information all you need to say is that the research is looking at experiences related to receiving an unlicensed 'special' medicine, that they have been selected because they are currently using an unlicensed 'special' medicine, and that they will receive a £15 high street voucher if they decide to take part in and complete an interview. If they wish to know more, or what to do next, our contact details are in the booklet, they can get in touch with us whenever they want.

After one complete month of providing patients with the information booklet and prepaid envelopes, we would be grateful if you could remind patients accessing unlicensed 'special' medicines about the research. You can do this by asking patients if you have already supplied them with a copy of the information booklet when they are next in the pharmacy to collect their medicine and providing more if needed.

If you agree to act as a gatekeeper and require copies of the information booklet and prepaid envelopes, or if you wish to discuss anything, please feel free to contact me at any time.

We look forward to hearing back from you,

Kind Regards,

Alesha Wale

Email: [EMAIL ADDRESS]

Tel: 07564247000





Dear [insert name here],

[ Date ]

We would like to invite you to act as a gatekeeper in our research regarding the use of unlicensed 'special' medicines. We are sending this letter to secondary care clinicians who prescribe medicines within dermatology, gastroenterology and paediatrics. As a gatekeeper we would like you to identify prescriptions for unlicensed 'special' medicines which will be discharged from secondary care into primary care. Before the patient is discharged from your care, we would like you to supply them with our information booklets and prepaid envelopes and explain that they are invited to participate in a study run by Cardiff University, looking at improving their experiences with their medicines. If you are asked for any further information all you need to say is that the research is looking at experiences related to receiving an unlicensed 'special' medicine, that they have been selected because they are currently using an unlicensed 'special' medicine, and that they will receive a £15 high street voucher if they decide to take part in and complete an interview. If they wish to know more, or what to do next, our contact details are in the booklet, they can get in touch with us whenever they want.

We would be grateful if you could inform patients that the research is looking at the experiences related to receiving an unlicensed 'special' medicine from a community pharmacy and the transition between care settings. Therefore, potential participants will have to wait until they have received their unlicensed 'special' medicine from a community pharmacy at least once before they can be eligible to take part in the study.

If you agree to act as a gatekeeper and require copies of the information booklet and prepaid envelopes, or if you wish to discuss anything, please feel free to contact me at any time.

We look forward to hearing back from you,

Kind Regards,

Alesha Wale

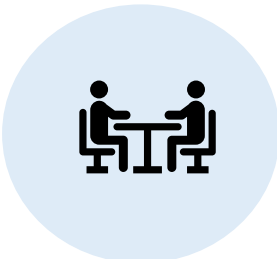
Email: [EMAIL ADDRESS]

Tel: 07564247000



# Are you or someone you care for using unlicensed “special” medicines?

Join us in a study to discuss your experiences and what further support you would like!



## What will I have to do?

Attend an interview to discuss how you obtain your special medicines and any problems you have

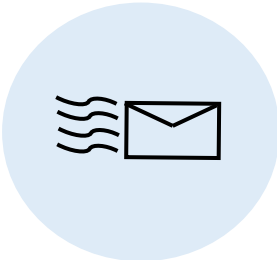
## Will I be compensated?

You will receive a £15 High street voucher for taking part in an interview.



## What should I do now?

Answer the questions in the back of this booklet and send us your replies using the pre-paid envelope. We will be in touch as soon as possible!



**We would like to invite you to take part in our study. Before you decide if you would like to take part, we would like you to understand why the study is being done and what it would involve for you.**

### **What is the study about?**

We are looking at unlicensed 'special' medicines that are dispensed from community pharmacies. We want to know about how you get your medicine from the pharmacy and how you feel about the medicine you take.



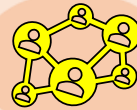
#### **Why have I been asked to take part?**

You have been invited because you, your child, or someone you care for, is currently using an unlicensed medicine.



#### **Do I have to take part?**

No, It's completely up to you! Your treatment will not be affected in any way whether you take part or not!



#### **Will the study help me?**

What you tell us will help us to understand how people who receive unlicensed medicines feel, which can lead to changes that can improve patients' experiences.



### **I am interested in taking part, what's next?**

Full information on the study is provided in the next few pages. Please complete **section A** of the card you will find in this booklet and return it in the prepaid envelope supplied. If you would like to take part in an interview over the phone, Skype or in person, please complete **section B** of the card in this booklet and provide your contact details. We will then get in touch with you.

## **Participant Information Sheet**

### **Title of project: Unlicensed ‘special’ medicines; Improving the patients’ experience**

We would like to invite you to take part in our study. Before you decide if you would like to take part, we would like you to understand why the study is being undertaken and what it would involve for you.

#### **What is the background of this study?**

Specials are unlicensed medicinal products manufactured in the UK for human use which have been specially prepared to meet a prescription ordered for individual patients without the need for the manufacturer to hold a marketing authorisation for the medicinal product concerned. Unlicensed ‘special’ medicines are used when no other licensed medication is available and although there are laws and regulations for their use in the UK, there is little evidence available on the experiences and perceptions of the patients who receive them. The project received funding by the Welsh European Funding Office (WEFO) and St. Mary’s Pharmaceuticals to explore patient experiences in relation to their special medicines.

#### **What is the purpose of the study?**

This study aims to explore what patients think about the process of accessing specials from a community pharmacy, highlight the impact of the medicines on the patients and give suggestions to improve the patient experience.

#### **Why have I been invited to participate?**

You have been invited because you, your child, or someone you care for, is currently using a prescription for an unlicensed ‘special’ medicine which has been dispensed through a community pharmacy.

#### **Do I have to take part?**

You are under no obligation to take part in the study; participation is voluntary and will not impact your treatment or the treatment of your child/person you are providing care for in any way.

#### **What do I have to do?**

If you wish to take part in the study, please complete section A of the card in the back of this booklet and return it in the prepaid envelope supplied. This will give us some background information on your medicine.

If you wish to take part in an interview and receive a £15 voucher for your time, then please also complete section B of the card in this booklet and return in the prepaid envelope supplied. You will then be invited to take part in an interview with the student researcher, Miss Alesha Wale. The interview will last around 10-20 minutes and will be conducted face-to-face in an agreed location, by telephone or via Skype. The interview will focus on the process of accessing special medicines from a community pharmacy, and your experiences with accessing and using specials.

If you agree to take part the researcher, Miss Alesha Wale, will contact you directly to discuss your preferred method of interview and arrange a suitable time to complete this. All interviews will be conducted in English. Before the interview takes place, you will be asked to sign two consent forms, one for the researcher to keep and the other is for you to keep. Following consent, the researcher will then proceed to start the interview. The interview will be audio recorded, written up as a transcript and then analysed, no names or identifying details will be mentioned in the transcripts or the final analysis. The audio tapes will be deleted immediately after transcription.

### **What happens next?**

Once you have completed the interview, you will receive the £15 gift voucher. The researcher will analyse the transcripts, look for recurring topics and recommendations will be suggested. The study will be written up to complete a thesis for a PhD with Cardiff University and results may be published in national and international conferences and journals. A report of the findings and any suggestions for improvement will be disseminated to St Mary's Pharmaceutical Unit (SMPU) and the steering group of the study. If you would like a copy of the report, please contact the research team (details below).

### **Will my participation in the study be kept confidential?**

Yes, the information provided will be kept strictly confidential by the researcher, all recordings will be destroyed after transcription, and all identifiable data will be anonymised in the final report. There will be no way

of linking comments made to individuals. Consent forms and completed cards will be stored securely at Cardiff University in accordance with the Data Protection Act 2018 for 15 years from the end of the study, with no way of connecting to individuals.

### **How will my personal data be managed?**

Staff at Cardiff University will only have access to your personal data if you give your consent to take part in the study. If you choose not to return the card in this booklet, or to only complete part A, then Cardiff University will not have access to your personal data.

Cardiff University is the sponsor of the study based in the UK. If you choose to take part in the study, we will be using information from you, your child or a person you are caring for in order to undertake this study and will act as the Data Controller for the study. This means that Cardiff University is responsible for looking after your information and using it properly. Cardiff University will keep identifiable information about you for 15 years after the study has ended.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study after data anonymisation has been completed, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. The legal basis upon which we are storing and processing your personal data is public task.

You can find out more about how we use your information at [www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection](http://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection). The University's Data Protection Officer can be contacted At [EMAIL ADDRESS]. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by

organisations and researchers to conduct research in accordance with the [UK Policy Framework for Health and Social Care Research](#).

### **What happens if I don't want to take part/carry on with the study?**

You are free to withdraw at any time, without giving a reason. This will not affect you in any way. If you withdraw before complete data anonymity has been reached the data collected from the interview will be destroyed and will not be analysed. However, if you withdraw once data anonymisation has been reached, it will be impossible to remove your data. **Who has reviewed the study?**

The study was reviewed and gained Sponsorship from Cardiff University on (Date) and ethical approval from the NHS on (Date)

### **What if there is a problem?**

If you have any concerns or complaints during the course of this research project, please contact Dr Efi Mantzourani who will address the issue. If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, [EMAIL ADDRESS].

### **How to contact us**

If there is anything that is not clear or if you would like more information, please contact the project supervisor, Dr Efi Mantzourani, or the researcher Miss Alesha Wale.

Dr Efi Mantzourani  
Cardiff School of Pharmacy  
and Pharmaceutical Sciences.  
Email: [EMAIL ADDRESS]  
Tel: 029-2087 0452

Miss Alesha Wale, BSc, MSc.  
Cardiff School of Pharmacy  
and Pharmaceutical Sciences.  
E-mail: [EMAIL ADDRESS]  
Tel: 07564247000



**Thank you very much  
for taking the time to  
read this information  
sheet!**



**Part A (please complete and send with the prepaid envelope)**

**What unlicensed medicine(s) are you currently receiving?**

**Do you use multiple pharmacies to collect your medicine (please circle)?**

Y / N

**Please name the pharmacy / pharmacies you use:**

**When was the first time you were prescribed an unlicensed medicine?**

Month: \_\_\_\_\_ Year: \_\_\_\_\_

**It was prescribed by...(please circle):** GP / Hospital Doctor / Other

If other, please specify: \_\_\_\_\_

**Please state your agreement with the following sentences (please circle).**

If you are completing this on behalf of someone else, please consider how they would reply.

**1. I was aware I was being prescribed a special the first time I received the medicine.**

Strongly Disagree	Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Agree	Strongly Agree
-------------------	----------	-------------------	----------------------------	----------------	-------	----------------

**2. I was given enough information about what a special medicine is.**

Strongly Disagree	Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Agree	Strongly Agree
-------------------	----------	-------------------	----------------------------	----------------	-------	----------------

**3. It was easy for me to access the medicine the first time from the pharmacy.**

Strongly Disagree	Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Agree	Strongly Agree
-------------------	----------	-------------------	----------------------------	----------------	-------	----------------



**4. I feel comfortable that my medicine is classified as a special.**

Strongly Disagree	Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Agree	Strongly Agree
-------------------	----------	-------------------	----------------------------	----------------	-------	----------------

**5. Taking a special medicine has overall improved my wellbeing.**

Strongly Disagree	Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Agree	Strongly Agree
-------------------	----------	-------------------	----------------------------	----------------	-------	----------------

**These questions help us categorise your answers.**

**What is your sex (please circle)?** F / M / Other / Prefer not to say

**What is your age?** \_\_\_\_\_

Please add anything else that you feel is relevant to your specials medicine.

**Part B (please complete this to take part in an interview)**

Name / Surname: \_\_\_\_\_

I am interested in taking part in an interview (please circle): Y / N

How would you like to be contacted by the researcher to make arrangements for the interview? Please circle your preferred choice and supply your contact information against it.

- Email (block capitals): \_\_\_\_\_
- Phone : \_\_\_\_\_

Most convenient for researcher to ring you (please circle):

Morning

Afternoon

Evening



## Participant Information Sheet

**Title of project: Unlicensed 'special' medicines; Improving the patients' experience**

IRAS ID: 268899

We would like to invite you to take part in our study. Before you decide if you would like to take part, we would like you to understand why the study is being undertaken and what it would involve for you.

### **What is the background of this study?**

Specials are unlicensed medicinal products manufactured in the UK for human use which have been specially prepared to meet a prescription ordered for individual patients without the need for the manufacturer to hold a marketing authorisation for the medicinal product concerned. Unlicensed 'special' medicines are used when no other licensed medication is available and although there are laws and regulations for their use in the UK, there is little evidence available on the experiences and perceptions of the patients who receive them. The project received funding by the Welsh European Funding Office (WEFO) and St. Mary's Pharmaceuticals to explore patient experiences in relation to their special medicines.

### **What is the purpose of the study?**

This study aims to explore what patients think about the process of accessing specials from a community pharmacy, highlight the impact of the medicines on the patients and give suggestions to improve the patient experience.

### **Why have I been invited to participate?**

You have been invited because you, your child, or someone you care for, is currently using a prescription for an unlicensed 'special' medicine which has been dispensed through a community pharmacy.

### **Do I have to take part?**

You are under no obligation to take part in the study; participation is voluntary and will not impact your treatment or the treatment of your child/person you are providing care for in any way.

### **What do I have to do?**

If you wish to take part in the study, please complete section A of the card in the back of this booklet and return it in the prepaid envelope supplied. This will give us some background information on your medicine.

If you wish to take part in an interview and receive a £15 voucher for your time, then please also complete section B of the card in this booklet and return in the prepaid envelope supplied. You will then be invited to take part in an interview with the student researcher, Miss Alesha Wale. The interview will last around 10-20 minutes and will be conducted face-to-face in an agreed location, by telephone or via Skype. The interview will focus on the process of accessing special medicines from a community pharmacy, and your experiences with accessing and using specials.

If you agree to take part the researcher, Miss Alesha Wale, will contact you directly to discuss your preferred method of interview and arrange a suitable time to complete this. All interviews will be conducted in English. Before the interview takes place, you will be asked to sign two consent forms, one for the researcher to keep and the other is for you to keep. Following consent, the researcher will then proceed to start the interview. The interview will be audio recorded, written up as a transcript and then analysed, no names or identifying details will be mentioned in the transcripts or the final analysis. The audio tapes will be deleted immediately after transcription.

### **What happens next?**

Once you have completed the interview, you will receive the £15 gift voucher. The researcher will analyse the transcripts, look for recurring topics and recommendations will be suggested. The study will be written up to complete a thesis for a PhD with Cardiff University and results may be published in national and international conferences and journals. A report of the findings and any suggestions for improvement will be disseminated to St

Mary's Pharmaceutical Unit (SMPU) and the steering group of the study. If you would like a copy of the report, please contact the research team (details below).

### **Will my participation in the study be kept confidential?**

Yes, the information provided will be kept strictly confidential by the researcher, all recordings will be destroyed after transcription, and all identifiable data will be anonymised in the final report. There will be no way of linking comments made to individuals. Consent forms and completed cards will be stored securely at Cardiff University in accordance with the Data Protection Act 2018 for 15 years from the end of the study, with no way of connecting to individuals.

### **How will my personal data be managed?**

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Cardiff University is the sponsor of the study based in the UK. If you choose to take part in the study, we will be using information from you, your child or a person you are caring for in order to undertake this study and will act as the Data Controller for the study. This means that Cardiff University is responsible for looking after your information and using it properly. Cardiff University will keep identifiable information about you for 15 years after the study has ended.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study after data anonymisation has been completed, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. The legal basis upon which we are storing and processing your personal data is public task.

You can find out more about how we use your information at [www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection](http://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection). The University's Data Protection Officer can be contacted at [EMAIL ADDRESS].

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### **What happens if I don't want to take part/carry on with the study?**

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### **Who has reviewed the study?**

The study was reviewed and gained Sponsorship from Cardiff University on (Date) and ethical approval from the NHS on (Date)

### **What if there is a problem?**

If you have any concerns or complaints during the course of this research project, please contact Dr Efi Mantzourani who will address the issue. If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, {EMAIL ADDRESS}.

### **How to contact us**

If there is anything that is not clear or if you would like more information, please contact the project supervisor, Dr Efi Mantzourani, or the researcher Miss Alesha Wale.

Version 4. Jan 2020.

Dr Efi Mantzourani  
Cardiff School of Pharmacy  
and Pharmaceutical Sciences.  
Email: [EMAIL ADDRESS]  
Tel: 029-2087 0452

Miss Alesha Wale, BSc, MSc.  
Cardiff School of Pharmacy  
and Pharmaceutical Sciences.  
E-mail: [EMAIL ADDRESS]  
Tel: 07564247000

**Thank you very much for taking the time to read this information sheet!**



IRAS ID: 268899

Study Number: 1

**Consent Form**

**Title of project: Unlicensed ‘special’ medicines; improving the patients’ experience**

Name of researcher: Alesha Wale

	Please initial box
1. I confirm that I have read and understood the participation information sheet dated August 2019 (Version 2.) provided for this study.	
2. I have been given opportunity to ask questions and these have been answered and explained to me.	
3. I am aware that this is a voluntary study and I may withdraw at any time, without giving reason and this will not affect my medical care or legal rights in any way.	
4. I understand that the information collected may be used to support other research and may be shared anonymously with other researchers.	
5. I agree to the interview being audio recorded.	
6. I agree to the use of anonymised, verbatim (‘word for word’) quotes in publications.	
7. I understand that the information collected will remain confidential and that any identifiers will be removed from any information used during the write up process.	
8. I agree if information is shared that suggests potential harm to myself or others, the researcher may pass along this information to a member of my healthcare team or general practitioner.	
9. I agree to take part in the above study	

Name of participant:

Name of person taking consent:

Date:

Date:

Signature:

Signature:

## Patient interview Schedule

Hello, thank you for taking the time to come and speak with me, I just want to confirm that you've read the information sheet and signed the consent form? Ok great, so before we begin, I thought I'd just give you an overview of what we'll be talking about today. I'll start with asking a few general questions, then I'll ask about the processes involved in accessing your medicine and then move on to some of the experiences you have had. Do you have any questions before we begin?

A = Has received special in secondary care. B= has only received special in primary care.

Question	Notes
<p><b>'Setting the scene'</b></p> <p>I can see (from the survey) that you/your [relative e.g. son/daughter/parent] have been using...[name of special]</p> <p>How long have you been receiving this unlicensed medicine?</p> <p>What do you understand about what an unlicensed medicine is?</p> <p>How do you feel about your medicine being classed as unlicensed?</p>	
<p><b>Q1. We will talk first about the first time you received [name of unlicensed medicine]?</b></p> <p><i>Can you tell me a bit about that?</i></p> <ul style="list-style-type: none"> <li>• <i>Where? In hospital or in community pharmacy?</i></li> <li>• <i>And were you informed at that time that you were being given an unlicensed medicine? Tell me about that.</i></li> </ul> <p><i>What information was discussed or given to you at that time about unlicensed medicines? Tell me about that.</i></p> <ul style="list-style-type: none"> <li>• <i>Who supplied you with this information? Hospital doctor/GP/pharmacist</i></li> <li>• <i>How to use e.g. shaking bottle really well</i></li> <li>• <i>How to store</i></li> <li>• <i>Short expiry date of product</i></li> <li>• <i>Importance of having same product from manufacturer every time</i></li> <li>• <i>Feelings about volume of information/ was it enough?</i></li> </ul>	<p>First prescribed/informed</p>

<p><b>A: Q2.1 If you received [name of unlicensed medicine] from hospital for the first time, tell me how you received further supplies once you were discharged from the hospital.</b></p> <p><i>Prompts:</i>  <i>Information about further supplies provided?</i>  <i>How did you order a new prescription?</i></p> <ul style="list-style-type: none"> <li>• <i>Need to go back to hospital or from GP</i></li> <li>• <i>If you had to order from GP, how long until you received the prescription</i></li> <li>• <i>Then how long until you received the supply from the pharmacy?</i></li> <li>• <i>Did you receive the same medication after discharge?</i></li> </ul> <p><b>B: Q2.2 If you received a prescription for [name of unlicensed medicine] from your GP for the first time, tell me about how you got the supply from the pharmacy. How long until you received the supply from the pharmacy?</b></p>	Transition (if applicable)
<p><b>Q3. Ok, now we will talk about your experiences with the pharmacy in general</b></p> <p><i>What information is being discussed with you when you are being supplied with [name of unlicensed medicine]? (do not duplicate info from Q1, if the answer there was a pharmacy). Does the pharmacist repeat information on...</i></p> <ul style="list-style-type: none"> <li>• <i>Making it clear that product is being ordered only for you</i></li> <li>• <i>How to use e.g. shaking bottle really well</i></li> <li>• <i>How to store</i></li> <li>• <i>Short expiry date of product and importance of ordering early</i></li> <li>• <i>Importance of having same product from manufacturer every time</i></li> </ul> <p><i>Can you tell me roughly how many times you have received your medicine from the community pharmacy?</i></p> <ul style="list-style-type: none"> <li>• <i>Have you been receiving the same medicine every time?</i></li> <li>• <i>How long does it take from the time you ask the GP for an updated prescription until you receive one</i></li> <li>• <i>And then how long from handing in your prescription at the pharmacy to receiving your medicine</i></li> <li>• <i>Have the pharmacy staff been helpful when accessing further supplies of your medicine?</i>  <i>Tell me about that</i></li> </ul>	Experiences receiving unlicensed medicines in primary care

<p><b>Q4. We will move on now to discuss your experiences with the medicine itself.</b></p> <p><i>Prompts:</i></p> <p><i>Do you know why you are taking it? (if it hasn't been covered before)</i></p> <p><i>Tell me about what you expected the medicine to do. Has it worked? How/why not?</i></p> <p><i>Have you experienced any problems with your medicine? Tell me about that.</i></p>	<p>Experiences with using the medicine</p>
<p><b>Q5 You have mentioned that you have been taking [name of unlicensed medicine] for ...months/years. In that time period, has the use of your medicine been reviewed? Tell me about that.</b></p> <p><i>Prompts:</i></p> <p><i>How often/how many times has this happened?</i></p> <p><i>What does this involve?</i></p> <p><i>Have any changes been made to your medicine due to a review e.g. strength, dose, brand, type?</i></p> <p>Do you know how long you will be receiving this medicine for?</p> <ul style="list-style-type: none"> <li>• Long-term need?</li> </ul>	<p>Review process (if applicable – even if never been reviewed, ask the last question)</p>
<p><b>Q6. Thank you very much for all of this. If I was to summarise the main points from our discussion, would you say an accurate summary would be...</b></p> <p>You are generally happy with....          For you, issues that you face are...          You also mentioned that you would prefer it if...</p> <p><i>What (other) change(s) would you like to see in the future [for the specific issue(s)]?</i></p> <p><i>Is there anything else you would like to add?</i></p> <p><i>Do you have any questions?</i></p>	<p>Summary</p>

Thank you for taking the time to meet with me today and discussing your experiences!



Version 2. May 2019.

**Study 2 Supporting documents.**

Cover letter for Gatekeepers in Primary care.

Cover letter for Gatekeepers in Secondary care.

Cover letter for Participants.

Participant Information Sheet.

Participant Consent Form.

Primary care Clinician Interview Schedule.

Secondary care Clinician Interview Schedule.



Dear [insert name here]

[Date]

We would like to invite you to act as a gatekeeper for our research regarding the use of unlicensed 'special' medicines. You will be required to disseminate copies of the cover letter, participant information sheet and pre-paid envelopes to General Practitioners with experience prescribing medicines, including unlicensed 'special' medicines.

One month after the initial dissemination of information, you will be required to remind potential participants about the research and supply further copies of the information sheet if needed.

If you agree to act as a gatekeeper and require copies of the information sheet or have any questions about the research, please feel free to contact me.

We look forward to hearing back from you,

Kind Regards,

Alesha Wale

Email: [EMAIL ADDRESS]

Tel: 07564247000



Dear [insert name here],

[Date]

Thank you for agreeing to act as a gatekeeper in our research into patient views and experiences regarding the use of unlicensed 'special' medicines.

We are also interested in the views and experiences of secondary care clinicians regarding prescribing unlicensed 'special' medicines and would like to invite you to participate in an interview. Please see attached an information sheet with details of the research and what it would involve. If you would like to take part in an interview, or if you know others who may be interested in participating and require extra copies of the information sheet, please do not hesitate to contact me. Anyone who takes part and completes the interview will be entered into a raffle with the chance to win a £15, £25 or £50 high street voucher.

We look forward to hearing back from you.

Kind Regards,

Alesha Wale

Email: [\[EMAIL ADDRESS\]](#)

Tel: 07564247000

Version 2. Jan 2020.



Dear [insert name here],

[Date]

Researchers at Cardiff University are conducting a study exploring the views and experiences of clinicians regarding prescribing unlicensed 'special' medicines. Based on your experience, we would like to invite you to participate in a short interview at a time of your convenience. All participants who complete the interview will be entered into a raffle with the chance to win a £15, £25 or £50 high street voucher.

Please see attached an information sheet with details of the research and what it would involve. If you would like to take part in an interview, please do not hesitate to contact me.

We look forward to hearing back from you.

Kind Regards,

Alesha Wale

Email: [EMAIL ADDRESS]

Tel: 07564247000



IRAS ID:268899

## Participant Information Sheet

### Title of project: Unlicensed 'special' medicines; improving the patients' experience

We would like to invite you to take part in our study. Before you decide if you would like to take part, we would like you to understand why the study is being undertaken and what it would involve for you.

#### What is the background of this study?

Unlicensed 'special' medicines are used when no other licensed medication is available and are often made to treat a specific individual. Specials are used around the world and although there are laws and regulations for their use in the UK, there is little evidence available on the experiences and perceptions of the healthcare professionals who prescribe them. The project received funding by the Welsh European Funding Office (WEFO) and St. Mary's Pharmaceuticals to explore key stakeholder views and experiences in relation to the use of unlicensed 'special' medicines; this study will focus on prescriber views.

#### What is the purpose of the study?

This study aims to explore the processes involved when prescribing unlicensed 'special' medicines in primary and secondary care and the views and experiences of the healthcare professionals who do this.

#### Why have I been invited to participate?

You have been invited because you work in primary or secondary care and have experience prescribing medicines, including unlicensed 'special' medicines.

#### Do I have to take part?

You are under no obligation to take part in the study; participation is voluntary.

#### What do I have to do?

If you wish to take part in an interview and be entered into a raffle with a chance to win a £15, £25 or £50 high street voucher, please contact the researcher Miss Alesha Wale directly (details below). The interview will last around 15-20 minutes and will be conducted face-to-face at your place of work, by telephone or via Skype. The interview will focus on the process of prescribing unlicensed 'special' medicines and your views and experiences related to this.

If you agree to take part, the researcher will contact you directly to discuss your preferred method of interview and arrange a suitable time to complete this. All interviews will be conducted in English. Before the interview takes place, you will be asked to sign two consent forms, one for the researcher to keep and the other is for you to keep. Following consent, the researcher will then proceed to start the interview. The interview will be audio recorded, written up as a transcript and then analysed, no names or identifying details will be mentioned in the transcripts or the final analysis. The audio tapes will be deleted immediately after transcription.

#### What happens next?

Once you have completed the interview, you will be entered into the raffle. The researcher will analyse the transcripts and look for recurring topics. Results will be triangulated with patient and pharmacist views, and recommendations will be suggested. The study will be written up to complete a thesis for a PhD with Cardiff University and results may be published in national and international conferences and journals. A report of the findings and any suggestions for improvement will be disseminated to St Mary's Pharmaceutical Unit (SMPU) and the steering group of the study. If you would like a copy of the report, please contact the research team (details below).

#### Will my participation in the study be kept confidential?

Yes, the information provided will be kept strictly confidential by the researcher, all recordings will be destroyed after transcription, and all identifiable data will be anonymised in the final report. There will be no way of linking Participant Information Sheet

comments made to individuals. Consent forms will be stored securely at Cardiff University in accordance with the Data Protection Act 2018 for 15 years from the end of the study, with no way of connecting to individuals.

### **How will my personal data be managed?**

Staff at Cardiff University will only have access to your personal data if you give your consent to take part in the study. Cardiff University is the sponsor of the study based in the UK. If you choose to take part in the study, we will be using information from you, in order to undertake this study and will act as the Data Controller for the study. This means that Cardiff University is responsible for looking after your information and using it properly. Cardiff University will keep identifiable information about you for 15 years after the study has ended.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study after data anonymisation has been completed, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. The legal basis upon which we are storing and processing your personal data is public task.

You can find out more about how we use your information at [www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection](http://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection). The University's Data Protection Officer can be contacted at [EMAIL ADDRESS].

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

When you agree to take part in a research study, the information gained may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the [UK Policy Framework for Health and Social Care Research](#).

### **What happens if I don't want to take part/carry on with the study?**

You are free to withdraw at any time, without giving a reason. This will not affect you in any way. If you withdraw before complete data anonymity has been reached the data collected from the interview will be destroyed and will not be analysed. However, if you withdraw once data anonymisation has been reached, it will be impossible to remove your data.

### **Who has reviewed the study?**

The study was reviewed and gained Sponsorship from Cardiff University on (Date) and ethical approval from the NHS on (Date)

### **What if there is a problem?**

If you have any concerns or complaints during the course of this research project, please contact Dr Efi Mantzourani who will address the issue. If you remain unhappy and wish to complain formally, you can do this by contacting the Director of Research, Cardiff School of Pharmacy and Pharmaceutical Sciences, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, [EMAIL ADDRESS].

### **How to contact us**

If there is anything that is not clear or if you would like more information, please contact the project supervisor, Dr Efi Mantzourani, or the researcher Miss Alesha Wale.

Dr Efi Mantzourani  
Cardiff School of Pharmacy  
and Pharmaceutical Sciences.  
Email: [EMAIL ADDRESS]  
Tel: 029-2087 0452

Miss Alesha Wale, BSc, MSc.  
Cardiff School of Pharmacy  
and Pharmaceutical Sciences.  
E-mail: [EMAIL ADDRESS]  
Tel: 07564247000

**Thank you very much for taking the time to read this information sheet!**



IRAS ID: 268899

Study Number: 2

**Consent Form****Title of project: Unlicensed 'special' medicines; improving the patients' experience**

Name of researcher: Alesha Wale

	Please initial box
1. I confirm that I have read and understood the participation information sheet dated August 2019 (Version 2.) provided for this study.	
2. I have been given opportunity to ask questions and these have been answered and explained to me.	
3. I am aware that this is a voluntary study and I may withdraw at any time, without giving reason and this will not affect my legal rights in any way.	
4. I understand that the information collected may be used to support other research and may be shared anonymously with other researchers.	
5. I agree to the interview being audio recorded.	
6. I agree to the use of anonymised, verbatim ('word for word') quotes in publications.	
7. I understand that the information collected will remain confidential and that any identifiers will be removed from any information used during the write up process.	
8. I agree if information is shared that suggests potential harm to myself or others, the researcher may pass along this information to a member of my healthcare team or general practitioner.	
9.. I agree to take part in the above study	

Name of participant:

Name of person taking consent:

Date:

Date:

Signature:

Signature:

**Prescriber (Primary care) Interview schedule**

Hello, thank you for taking the time to come and speak with me, I just want to confirm that you've read the information sheet and signed the consent form? Ok great, so before we begin, I thought I'd just give you an overview of what we'll be talking about today. I'll start with asking a few general questions, then I'll ask about the processes involved in prescribing unlicensed 'special' medicines and then move on to some of the experiences you have had. Do you have any questions before we begin?

Question	Notes
<p><b>'Setting the Scene'</b></p> <p>How long have you been a registered GP?</p> <p>Do you have any experience working in any other sector? If yes, where would that be?</p> <p>Can you tell me how you would define an unlicensed 'special' medicine?</p> <p>How do you feel about the safety and efficacy of unlicensed medicines?</p> <p>How do you feel about your role or responsibility in prescribing unlicensed 'special' medicines to patients?</p> <p>On average, how many unlicensed special medicines would you say you prescribe a month?</p> <p>What are the main cohorts of patients or diseases that your bulk of prescribing of unlicensed products relates to?</p> <p>Can you tell me the approx. % of unlicensed medicines you prescribed are initiated by a secondary care consultant compared to initiated by you?</p>	
<p><b>Q1. Decision-making processes</b>  <b>Q1.1. Let's start with when the therapy is initiated by you....</b></p> <p><b>Can you tell me about your decision-making process?? What factors do you consider as important?</b></p> <p><i>Prompt: Are there any additional clinical or professional checks that you undertake when you prescribe an unlicensed medicine, or is there a need to consult specific guidelines?</i></p> <p><i>How about supplier for the unlicensed medicine?</i></p> <p><i>How about cost?</i></p>	



**Q1.2 Let's move on to when the therapy has been specialist recommended or specialist initiated. Can you tell me about your decision making process in that case?**

*Prompt: Can you tell me about information that you may receive from secondary care regarding the unlicensed medicine e.g. formulation, strength, dosage?*

*How about reasons for recommending an unlicensed medicine?*

*How about the supplier?*

*Are there any additional clinical or professional checks that you undertake when you prescribe an unlicensed medicine that was specialist initiated or recommended, or is there a need to consult specific guidelines?*

*Thinking of all medicines that patients have on discharge, can you estimate the number of products that's unlicensed per week?*

*From them how many have the relevant follow-on prescribing information provided by the hospital? e.g. reason, details of product, special arrangements for continuity...*

**Q1.3 Can you tell me a little bit about the need for reviewing therapy for a special that was initiated previously?**

*Prompt: How about timelines? How often do you usually review a previously initiated therapy with an unlicensed medicine?*

*How about process? How do you monitor patients receiving an unlicensed medicine?*

*How about resources you may use to support you?*

**Q2. The next question is about ways with which you support patients who receive unlicensed medicines.**

**Can you tell me about any information you might provide to patients when you prescribe an unlicensed medicine? Compared to licensed?**

*How about information to inform the patient that they are receiving an unlicensed medicine and what that "means"*

*Can you tell me about your perception of patient attitudes/awareness towards the fact that they have been receiving an unlicensed medicine?*

<p><b>Q3. The last question is about potential issues you may face associated with unlicensed medicines.</b></p> <p><b>Can you tell me about your experiences with that?</b></p> <p><i>Prompt: How about patients transferring into primary care who were unable to access the specific formulation or dosage of the medicine initiated or recommended by a specialist?</i></p> <p><i>How about communication with community pharmacists about supplier issues?</i></p> <p><i>How about communication with community pharmacists about cost?</i></p> <p><i>Have you ever had a situation in which you have refused to prescribe an unlicensed medicine? Why was this?</i></p> <p><i>Have you ever had to report an ADR due to the use of an unlicensed medicine? Tell me about that.</i></p>	
<p><b>Q4. Thank you very much for all this. If I was to summarise the main points from our discussion, would you say an accurate summary would be...</b></p> <p><b>You are in general happy with...</b></p> <p><b>You would feel more comfortable if ....</b></p> <p><b>Is there anything else you think could improve the process?</b></p> <p><i>Prompt: Are there any important issues you feel need to be targeted?</i></p> <p><i>Is there anything you would like to add?</i></p> <p><i>Do you have any questions?</i></p>	

Thank you very much for taking the time to meet with me today and discuss your experiences!

**Prescriber (Secondary care) Interview schedule**

Hello, thank you for taking the time to come and speak with me, I just want to confirm that you've read the information sheet and signed the consent form? Ok great, so before we begin, I thought I'd just give you an overview of what we'll be talking about today. I'll start with asking a few general questions, then I'll ask about the processes involved in prescribing unlicensed 'special' medicines and then move on to some of the experiences you have had. Do you have any questions before we begin?

Question	Notes
<p><b>'Setting the Scene'</b></p> <p>How long have you been registered as a doctor?</p> <p>And how long have you been practising in secondary care?</p> <p>Do you have any experience working in any other sector? If yes, where would that be?</p> <p>Can you tell me how you would define an unlicensed 'special' medicine?</p> <p>How do you feel about the safety and efficacy of unlicensed medicines?</p> <p>How do you feel about your role or responsibility in prescribing unlicensed 'special' medicines to patients?</p> <p>On average, how many unlicensed special medicines would you say you prescribe a month?</p> <p>What are the main cohorts of patients or diseases that your bulk of prescribing of unlicensed products relates to?</p>	
<p><b>Q1.1. Now I would like to ask some questions related to when you initiate treatment with an unlicensed medicine for a patient</b></p> <p><i>Prompt: Can you tell me about how easy it is to know whether the product you want to prescribe is licensed or unlicensed?</i></p> <p><i>How about resources to support you?</i></p> <p><i>Can you tell me about your decision-making process? What factors do you consider as important?</i></p> <p><i>What are your reasons about choosing an unlicensed vs licensed product? How about cost?</i></p>	

<p><i>How about supplier for the unlicensed medicine?</i></p> <p><i>Are there any additional things you think about or checks you make when you prescribe an unlicensed medicine? How about specific guidelines?</i></p> <p><b>Q1.2 Ok, you have initiated treatment with an unlicensed medicine, and the patient is about to be discharged.</b></p> <p><b>Can you tell me about the process you go through?</b></p> <p><i>Prompt: How about when then patient continues to require a prescription for an unlicensed medicine?</i></p> <p><i>How about any standard discharge paperwork to ensure continuity of supply and quality of the unlicensed product e.g. formulation, strength, dosage and supplier?</i></p> <p><i>Are you able to approximately estimate the number of products of unlicensed medicines that patients have on discharge?</i></p> <p><b>Q1.3 Can you tell me a little bit about the need for reviewing therapy for a special that was initiated previously?</b></p> <p><i>Prompt: How about timelines? How often do you usually review a previously initiated therapy with unlicensed medicines?</i></p> <p><i>How about process? How do you monitor patients receiving an unlicensed medicine?</i></p> <p><i>How about resources you may use to support you?</i></p>	
<p><b>Q2. The next question is about ways with which you support patients who receive unlicensed medicines.</b></p> <p><b>Can you tell me about any information you might provide to patients when you prescribe an unlicensed medicine? Compared to licensed?</b></p>	

<p><i>Prompt: How about information to inform the patient that they are receiving an unlicensed medicine and what that “means”</i></p> <p><i>Can you tell me about your perception of patient attitudes/awareness towards the fact that they have been receiving an unlicensed medicine?</i></p>	
<p><b>Q3. The last question is about potential issues you may face associated with unlicensed medicines.</b></p> <p><b>Can you tell me about your experiences with that?</b></p> <p><i>Do your patients ever come back to you and tell you that they are having issues accessing an unlicensed medicine that you have prescribed in hospital?</i></p> <p><i>e.g. the specific formulation or dosage of the medicine that you prescribed?</i></p> <p><i>How about communication with GPs or community pharmacists about supplier issues with the unlicensed medicines ?</i></p> <p><i>How about discussions with GPs or community pharmacists about cost?</i></p> <p><i>Have you ever had to report an ADR due to the use of an unlicensed medicine? Tell me about that.</i></p>	
<p><b>Q4. Thank you very much for all this. If I was to summarise the main points from our discussion, would you say an accurate summary would be...</b></p> <p><b>You are in general happy with...</b></p> <p><b>You would feel more comfortable if ....</b></p> <p><b>Is there anything else you think could improve the process?</b></p>	

<p><i>Prompt: Are there any important issues you feel need to be targeted?</i></p> <p><i>Is there anything you would like to add?</i></p> <p><i>Do you have any questions?</i></p>	
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Thank you very much for taking the time to meet with me today and discuss your experiences

## **Appendix 7. Reflections on conducting research during the Covid-19 pandemic**

Although it was originally planned for all participants to have the option to take part in an interview online if preferred, the impact of the Covid-19 pandemic resulted in the need to conduct all interviews in study 2 and 3 virtually. This differed to study 1 in which all participants chose to take part in an interview face to face. The use of online interviews during the Covid-19 pandemic has been suggested within the literature to ensure research and data collection can continue (Adom, Osei and Adu-Agyem 2020). However, prior to the Covid-19 pandemic the literature had already explored the use of online interviews, and had suggested that although online interviews were reported to take longer to conduct than face to face interviews, that the quality of the data gained was not impacted by the method used (Shapka *et al.*, 2016). Although evidence has shown that those who have taken part in online interviews have reported difficulties associated with the use of technology, they have also reported an overall positive experience (Mirick and Wladkowski, 2019) and since the pandemic began, findings from a review have supported the benefit of online interviews, suggesting that this method of data collection has been able to provide rich data and insight (Nind, Coverdale and Meckin, 2021). The researcher viewed the use of online interviews to be valuable and did not feel as though the rapport built during interviews or the level of detail discussed differed between the interviews conducted in person in study 1 and the interviews conducted online in studies 2 and 3. Although some challenges were faced with technology, the researcher felt this was easily overcome by describing in detail how the interviewee could take part and providing supporting emails prior to the start of the interview.

The researcher had previous experience conducting semi-structured interviews during their MSc and so felt comfortable conducting interviews in this manner in general. However, the researcher was nervous at the start of data collection due to the complex nature of the use of unlicensed medicines. The researcher gained feedback from the academic supervisor after the first two interviews to improve their interview technique and felt more comfortable as they gained more experience conducting interviews on this topic. When the project was extended to the full PhD the researcher took part in three workshops aimed at further improving their interviewing technique. One was accessed through the doctoral academy, the other two were organised by NatCen Social Research and were focussed on qualitative interviews and managing challenging interviews. This further helped to increase the researcher's confidence in their ability to conduct in-depth interviews and manage any difficult situations that may have arose. The researcher also perceived that their previous experience working with the public facilitating anxiety and depression sessions at Swansea

Mind also helped to increase their confidence when talking to members of the public and building rapport during interviews.

The sample sizes gained were clearly affected by the restrictions imposed during the Covid-19 pandemic which resulted in a reduced recruitment period. This coupled with the fact that many healthcare professionals were faced with increased workloads, could have reduced the number of potential participants contacted and who were able to take part. The researcher viewed this delay to be disadvantageous to the research process and contributed directly to the small sample sizes gained in study 2 and 3. This caused the researcher to be anxious about recruitment and unsure as to whether sufficient numbers could be gained in time. However, the researcher also accepts that when conducting research, a number of limitations are inevitable (see 7.6) and so in this way, these experiences provided the researcher with the opportunity to face challenges and alter the research approaches in order to overcome these, such as moving to online interviews only.

The impact of Covid-19 also resulted in the need for remote working in general which meant that much of the final write up of results were undertaken in the researcher's home. The researcher perceived advantages and disadvantages of the need to work from home. This included saving time by not needing to travel into the University or to conduct interviews across Wales. However, as the pandemic went on, the researcher realised that remote working limited the overall experience of conducting interviews and writing the thesis, by limiting the amount of time the researcher could interact with others, be that other PhD candidates, or members of the public. Although this was a necessity given the state of the pandemic at the time, and although the researcher did not feel as though they had missed out on anything vital during the course of the PhD, it was perceived that further engagement with the school would have been a positive experience.



## Appendix 8. Ethical approvals gained and amendments submitted

SPPS Amendment Approval Notification (AAN)

11/10/14 v1

<b>Cardiff School of Pharmacy and Pharmaceutical Sciences, Research Ethics Approval</b>
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### AMENDMENT APPROVAL

This form has been signed by the School Research Ethics Officer as evidence that approval has been granted by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee for amendment(s) to the following study:

Project ref and title:	<u>1718-28: Unlicensed 'special' medicines; improving the patients' experience</u>
------------------------	--


Name of researcher: (PG/Staff projects only)	<u>Alesha Wale</u>
Name of supervisor(s):	<u>Dr Efi Manztourani &amp; Dr Rowan Yemm</u>

The amendment(s) dated 31 July 2020 have been reviewed and approved.

Any further amendments will require approval.

### STATEMENT OF ETHICS APPROVAL

**The proposed amendment(s) have been considered and approved by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee**

Signed  Date 12/08/2020  
(Deputy Chair, School Research Ethics Committee)



Research and  
Innovation Services  
Gwasanaethau Ymchwil  
ac Arloesi

Cardiff University  
McKenzie House, 7<sup>th</sup> Floor  
30-36 Newport Road, Cardiff  
CF24 0DE, Wales, UK



Prifysgol Caerdydd  
Tŷ McKenzie, 7<sup>th</sup> Llawr  
30-36 Heol Casnewydd, Caerdydd  
CF24 0DE, Cymru, DU



6<sup>th</sup> August 2019

Dr Efi Mantzourani  
School of Pharmacy and Pharmaceutical Sciences  
Cardiff University  
Redwood Building  
King Edward VII Avenue  
Cardiff  
CF10 3NB

Dear Dr Mantzourani,

### Unlicensed 'special' medicines: improving patients' experience

I understand that you are acting as Chief Investigator and Academic Supervisor for the above PhD project to be conducted by Alesha Wales.

I confirm that Cardiff University agrees in principle to act as Sponsor for the above project, as required by the UK Policy Framework for Health and Social Care Research.

#### Scientific Review

I can also confirm that Scientific Review has been obtained from: the Wales European Funding Office (WEFO) Knowledge Economy Skills Scholarship funding programme (KESS2).

#### Insurance

The necessary insurance provisions will be in place prior to the project commencement. Cardiff University is insured with UMAL. Copies of the insurance certificate are attached to this letter.

#### Approvals

On completion of your IRAS form (required for NHS REC and HRA/HCRW/NHS R&D permission), you will be required to obtain signature from the Research Governance team for the 'Declaration by the Sponsor Representative'. Please note that you are also required to provide the Organisation Information Document and Schedule of Events to the Research Governance team for review prior to submission to HRA/HCRW.

Please then submit the project to the following bodies for approval:

- an NHS Research Ethics Committee;
- Health & Care Research Wales (HCRW)- to arrange HRA/HCRW Approval for Welsh NHS sites.
- Mayberry Pharmacies (to obtain permission to commence the study).

The University is considered to have accepted Sponsorship when Research and Innovation Services has received evidence of the above approvals. **Responsibility for providing the Local Information Pack to NHS organisations is delegated from the Sponsor to the Chief Investigator (or their appropriate delegate). Once an NHS organisation has confirmed capacity and capability, responsibility lies with the Chief Investigator (or their appropriate delegate) to follow an appropriate 'green light' procedure to open the study at that Site.**

#### Roles and Responsibilities

As Chief Investigator you have signed a Declaration with the Sponsor to confirm that you will adhere to the standard responsibilities as set out by the UK Policy Framework for Health and Social Care Research. In



Registered Charity, no. 1136855  
Eusen Gofystredig, rhif 1136855

accordance with the University's Research Integrity & Governance Code of Practice, the Chief Investigator is also responsible for ensuring that each research team member is qualified and experienced to fulfil their delegated roles including ensuring adequate supervision, support and training.

If your study is adopted onto Health & Care Research Wales Clinical Research Portfolio you are required to upload recruitment data onto the portfolio database.

#### **Contracts**

- The HRA/HCRW Organisation Information Document will act as the agreement between the sponsor and participating NHS organisations.

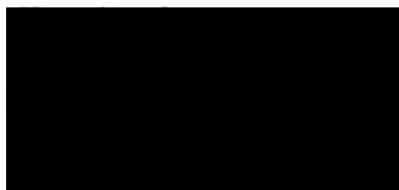
May I take this opportunity to remind you that, as Chief Investigator, you are required to:

- register clinical trials in a publicly accessible database before recruitment of the first participant and ensure that the information is kept up to date
- ensure you are familiar with your responsibilities under the UK Policy Framework for Health and Social Care Research;
- undertake the study in accordance with Cardiff University's Research Integrity & Governance Code of Practice (available on the Cardiff University Staff and Student Intranet) and the principles of Good Clinical Practice;
- ensure the research complies with the General Data Protection Regulation 2016/679;
- where the study involves human tissue, ensure the research complies with the Human Tissue Act and the Cardiff University Code of Practice for Research involving Human Tissue (available on the Cardiff University Staff and Student Intranet);
- inform Research and Innovation Services of any amendments to the protocol or study design, (including changes to start /end dates) and submit amendments to the relevant approval bodies;
- respond to correspondence from the REC, HRA/HCRW and NHS organisation R&D offices within the required timeframes;
- co-operate with any audit, monitoring visit or inspection of the project files or any requests from Research and Innovation Services for further information.

You should quote the following unique reference number in any correspondence relating to Sponsorship for the above project:

**SPON 1694-18**

This reference number should be quoted on all documentation associated with this project.



Cc Miss Alesha Wale (student).



Ymchwil Iechyd  
a Gofal **Cymru**  
Health and Care  
Research **Wales**



Dr Efi Mantzourani  
Redwood building  
King Edward VII Avenue  
Cardiff  
CF10 3NB



23 December 2019

Dear Dr Mantzourani

**HRA and Health and Care  
Research Wales (HCRW)  
Approval Letter**

**Study title:** Unlicensed 'special' medicines; improving the patients' experience.  
**IRAS project ID:** 268899  
**Protocol number:** SPON1694-18  
**REC reference:** 19/NW/0598  
**Sponsor** Cardiff University

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

**How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?**

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

**How should I work with participating non-NHS organisations?**

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to [obtain local agreement](#) in accordance with their procedures.

**What are my notification responsibilities during the study?**

The standard conditions document "[After Ethical Review – guidance for sponsors and investigators](#)", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The [HRA website](#) also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

**Who should I contact for further information?**

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **268899**. Please quote this on all correspondence.

Yours sincerely,

Michael Pate  
Approvals specialist

Email: [REDACTED]

Copy to: *Miss Helen Falconer*

## List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [Social Media Advert]	1	31 May 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		01 August 2019
Interview schedules or topic guides for participants [Participant Interview Schedule Study 1]	2	31 July 2019
Interview schedules or topic guides for participants [Primary care Clinician Interview Schedule Study 2]	2	31 July 2019
Interview schedules or topic guides for participants [Secondary care Clinician Interview Schedule Study 2]	2	31 July 2019
IRAS Application Form [IRAS_Form_23082019]		23 August 2019
Letter from funder [Kess 2 Agreement]		22 May 2019
Letter from sponsor [Sponsorship letter]		06 August 2019
Letters of invitation to participant [Cover letter for Secondary Care Gatekeepers Study 2]	1	31 May 2019
Letters of invitation to participant [Invitation to participate Study 2]	1	31 May 2019
Letters of invitation to participant [Cover Letter for Primary Care Gatekeepers Study 1]	2	01 August 2019
Letters of invitation to participant [Cover Letter for Secondary Care Gatekeepers Study 1.]	2	01 August 2019
Letters of invitation to participant [Cover letter for Primary Care Gatekeepers Study 2]	2	01 August 2019
Letters of invitation to participant [Clean Participant Information Booklet]	3	23 September 2019
Non-validated questionnaire [Participant Survey Study 1]	2	01 August 2019
Organisation Information Document [Organisation Information Document]		
Other [Protocol accepted changes]	3	24 September 2019
Other [Response to comments ]	1	23 September 2019
Participant consent form [Consent Study 1]	2	01 August 2019
Participant consent form [Consent Study 2]	2	01 August 2019
Participant information sheet (PIS) [PIS Study 1 clean]	3	23 September 2019
Participant information sheet (PIS) [PIS Study 2 Clean]	3	23 September 2019
Schedule of Events or SoECAT [Assessed - Schedule of Events]	1	04 September 2019
Summary CV for Chief Investigator (CI) [Summary CV]		14 August 2019
Summary CV for student [Summary CV]		19 August 2019
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Protocol Flow]	1	31 July 2019

IRAS project ID	268899
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### Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
One site type.	<b>Formal confirmation.</b> Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	<b>Organisation information document acts as the agreement</b> An organisation information document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Supplies provided to sites as per the Organisation Information Document.	Local PI.	Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

### Other information to aid study set-up and delivery

<i>This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.</i>
This study has not been put forward for adoption to the NIHR Portfolio, as it only involves Welsh sites, but will be assessed automatically for eligibility to the Welsh Portfolio.



Ymchwil Iechyd  
a Gofal Cymru  
Health and Care  
Research Wales



GIG  
CYMRU  
NHS  
WALES

Bwrdd Iechyd Prifysgol  
Aneurin Bevan  
University Health Board

R&D Department  
Clinical Research &  
Innovation Centre  
St Woolos Hospital  
Block C, Stow Hill  
Newport, South Wales  
NP20 4SZ

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## Research and Development Department



Miss Alesha Wale  
Doctoral Student  
School of Pharmacy and Pharmaceutical Science  
Cardiff University  
Redwood Building  
King Edward Ave VII  
Cardiff  
CF10 3NB

1 April 2021

Dear Miss Wale,

### Letter of access for research project:

**Title:** Unlicensed 'special' medicines; improving the patients' experience  
**Chief Investigator:** Dr Efi Mantzourani  
**Principal Investigator:** Alesha Wale  
**R&D Reference Number:** AB/70  
**IRAS Number:** 268899

We are satisfied that such checks as are necessary have been carried out by your employer and that the research activities that you will undertake in this NHS organisation are commensurate with the activities you undertake for your employer. This letter confirms your right of access to conduct research through the **Aneurin Bevan University Health Board** for the purpose and on the terms and conditions set out below.

For R&D reference number **AB/70** this right of access commences on the **13<sup>th</sup> February 2020** and ends on **30 June 2021**, unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project. You are considered to be a legal visitor to **Aneurin Bevan University Health Board** premises. You are not entitled to any form of payment or access to other



benefits provided by this organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **Aneurin Bevan University Health Board**, you will remain accountable to your employer, **Cardiff University**, but you are required to follow the reasonable instructions of your nominated manager **Jeanette Wells in ABUHB** or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **Aneurin Bevan University Health Board** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **Aneurin Bevan University Health Board** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **Aneurin Bevan University Health Board** premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution. **Aneurin Bevan University Health Board** will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct

or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the organisation that employs you through its normal procedures. You must also inform your nominated manager.

Yours sincerely



**Professor Sue Bale**  
**R&D Director**  
**Aneurin Bevan University Health Board**



Bwrdd Iechyd Prifysgol  
Caerdydd a'r Fro  
Cardiff and Vale  
University Health Board

**Ysbyty Athrofaol Cymru  
University Hospital of Wales**

Heath Park,  
Cardiff, CF14 4XW  
Phone 029 2074 7747  
Fax 029 2074 3838  
Minicom 029 2074 3632

Parc Y Mynydd Bychan,  
Caerdydd, CF14 4XW  
Ffôn 029 2074 7747  
Ffacs 029 20743838  
Minicom 029 2074 3632

Tel: [REDACTED]

From: R&D Office, 2<sup>nd</sup> Floor TB2  
University Hospital of Wales  
Cardiff  
CF14 4XW

10 March 2021

Ms Alesha Mary Wale  
4 Shirley Road  
Cardiff  
CF23 5HN

Dear Ms Wale,

**Letter of access for research issued by Cardiff and Vale University Health Board**

R&D Ref	IRAS Ref	Study title	Agreed duties
20/JAN/7833	268899	Unlicensed 'special' medicines; Improving the patients' experience.	Participant Identification, supply of study information, signing Informed consent and taking part in Interviews.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on **01 April 2021** and ends on **31 July 2021 (planned study end date)** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from Cardiff and Vale UHB. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation(s) of their agreement to conduct the research.

The information supplied about your role in research at Cardiff and Vale University Health Board has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Cardiff and Vale University Health Board premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Cardiff and Vale University Health Board, you will remain accountable to your substantive employer, **Cardiff University**, but you are required to follow the reasonable instructions of your supervisor in this organisation, **the Local Collaborators, Dr John Ingram, Dr Phillip Connor and a Local Collaborator from Gastroenterology**, or those given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Cardiff and Vale University Health Board policies and procedures, which are available to you upon request, and the Research Governance Framework.

Bwrdd Iechyd Prifysgol Caerdydd a'r Fro yw enw gweithredol Bwrdd Iechyd Lleol Prifysgol Caerdydd a'r Fro  
Cardiff and Vale University Health Board is the operational name of Cardiff and Vale University Local Health Board



LoA for university researchers, v2.5

You are required to co-operate with Cardiff and Vale University Health Board in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Cardiff and Vale University Health Board premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and Cardiff and Vale University Health Board Research and Development Office prior to commencing your research role at the Health Board.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

This organisation may revoke this letter and any organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 2018. Any breach of the Data Protection Act 2018 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in each participating NHS organisation and the R&D office in this organisation.

Yours sincerely



**Registration and Permissions Improvement Manager  
On behalf of Cardiff and Vale University Health Board**

cc: HR department of the substantive employer  
Supervisor at Cardiff and Vale UHB

**Attachment:** Mandatory training requirements for HRC/LoA



GIG  
CYMRU  
NHS  
WALES

Bwrdd Iechyd Prifysgol  
Hywel Dda  
University Health Board

Ein cyfr/Our ref: PNR/P  
Gofynnwch am/Please ask for: Petra Newman  
Rhif Ffôn /Telephone: [REDACTED]  
Ffacs/Facsimile: [REDACTED]  
E-bost/E-mail: [REDACTED]  
Dyddiad/Date: 24<sup>th</sup> February 2020

Ysbyty Cyffredinol Llwynhelig  
Heol Abergwaun, Hwlfordd,  
Sir Benfro, SA61 2PZ  
Rhif Ffôn: 01437 764545

Withybush General Hospital  
Fishguard Road, Haverfordwest,  
Pembrokeshire, SA61 2PZ  
Tel: 01437 764545

**PRIVATE AND CONFIDENTIAL**

Miss Alesha Wale  
Doctoral Student  
Cardiff University  
School of Pharmacy & Pharmaceutical Sciences  
Redwood Building  
King Edward Avenue VII  
Cardiff  
CF10 3NB

Dear Miss Wale

**Letter of access for research  
Unlicensed 'special' medicines; Improving the patients' experience  
Ref: 268899**

This letter should be presented to each participating organisation before you commence your research at that site.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on 24<sup>th</sup> February 2020 and ends on 28<sup>th</sup> February 2021 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation of their agreement to conduct the research.

The information supplied about your role in research at the organisation has been reviewed and you do not require an honorary research contract with the organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. Evidence of checks should be available on request.

You are considered to be a legal visitor to the organisation's premises. You are not entitled

Swyddfeydd Corfforaethol, Adeilad Ystwyth,  
Hafan Derwen, Parc Dewi Sant, Heol Ffynnon Job,  
Caerdyddin, Sir Gaerdyddin, SA31 3BB

Corporate Offices, Ystwyth Building,  
Hafan Derwen, St Davids Park, Job's Well Road,  
Carmarthen, Carmarthenshire, SA31 3BB

Cadeirydd /Chair  
Miss Maria Battle  
Prif Weithredwr/Chief Executive  
Mr Steve Moore

Bwrdd Iechyd Prifysgol Hywel Dda yw enw gweithredol Bwrdd Iechyd Lleol Prifysgol Hywel Dda  
Hywel Dda University Health Board is the operational name of Hywel Dda University Local Health Board

Mae Bwrdd Iechyd Prifysgol Hywel Dda yn amgylchedd di-fwg Hywel Dda University Health Board operates a smoke free environment

to any form of payment or access to other benefits provided by the organisation to employees and this letter does not give rise to any other relationship between you and the organisation, in particular that of an employee.

While undertaking research through the organisation you will remain accountable to Cardiff University but you are required to follow the reasonable instructions of Chris Tattersall, R&D Manager, or those instructions given on his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with the organisation's policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with the organisation in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisation's premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your supervisor at Cardiff University and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 2018. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the organisation's premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation do not accept responsibility for damage to or loss of personal property.

This organisation may revoke this letter and any organisation may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Cardiff University will immediately withdraw you from undertaking this or any other regulated activity and you **MUST** stop undertaking any regulated activity immediately.

Cardiff University is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 2018. Any breach of the Data Protection Act 2018 may result in legal action against you and/or Cardiff University.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform Cardiff University through their normal procedures. You must also inform your nominated manager in each participating organisation and Chris Tattersall, R&D Manager, in this organisation.

Yours sincerely

A black rectangular redaction box covering the signature of the Senior Workforce Manager.

**Senior Workforce Manager**

**Copied to: Chris Tattersall, R&D Manager, Hywel Dda University Health Board  
Dr Efi Mantzourani, Senior Lecturer in Pharmacy Practice, Cardiff  
University**



Bwrdd Iechyd Prifysgol  
Hywel Dda  
University Health Board

Ein cyf/Our ref: PN/RP  
Gofynnwch am/Please ask for: Petra Newman  
Rhif Ffôn /Telephone: [REDACTED]  
Ffacs/Facsimile: [REDACTED]  
E-bost/E-mail: [REDACTED]  
Dyddiad/Date: 31<sup>st</sup> March 2021

Ysbyty Cyffredinol Llwynhelyg  
Heol Abergwaun, Hwlfordd,  
Sir Benfro, SA61 2PZ  
Rhif Ffôn: 01437 764545

Withybush General Hospital  
Fishguard Road, Haverfordwest,  
Pembrokeshire, SA61 2PZ  
Tel: 01437 764545

**Private and Confidential**

Miss Alesha Wale  
Doctoral Student  
Cardiff University  
School of Pharmacy & Pharmaceutical Sciences  
Redwood Building  
King Edward Avenue VII  
Cardiff  
CF10 3NB

Dear Miss Wale

**Letter of access for research**

**Unlicensed 'special' medicines; Improving the patients' experience**

**Ref: 268899**

With reference to your Letter of Access which expired on 28<sup>th</sup> February 2021, we can now confirm that this has been extended until 31<sup>st</sup> June 2021.

Yours sincerely



**Senior Workforce Manager**

**Copied to: Chris Tattersall, R&D Manager, Hywel Dda University Health Board  
Dr Efi Mantzourani, Senior Lecturer in Pharmacy Practice, Cardiff  
University**

Swyddfeydd Corfforaethol, Adeilad Ystwyth,  
Hafan Derwen, Parc Dewi Sant, Heol Ffynnon Job,  
Caerdyddin, Sir Gaerdyddin, SA31 3BB

Corporate Offices, Ystwyth Building,  
Hafan Derwen, St Davids Park, Job's Well Road,  
Carmarthen, Carmarthenshire, SA31 3BB

Cadeirydd /Chair  
**Miss Maria Battle**  
Prif Weithredwr/Chief Executive  
**Mr Steve Moore**

Bwrdd Iechyd Prifysgol Hywel Dda yw enw gweithredol Bwrdd Iechyd Lleol Prifysgol Hywel Dda  
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Mae Bwrdd Iechyd Prifysgol Hywel Dda yn amgylchedd di-fwg Hywel Dda University Health Board operates a smoke free environment





Cadeirydd/Chairman: **Andrew Davies**  
Prif Weithredwr/Chief Executive: **Tracy Myhill**

gofalu am ein gilydd, cydweithio, gwella bob amser  
caring for each other, working together, always improving

Rydym yn croesawu gohebiaeth yn y Gymraeg ac yn y Saesneg. We welcome correspondence in Welsh or English.

☎ Direct line/Rhif Ilinell union: 01792 957585

Research & Development Department  
Swansea Bay University Health Board  
ILS 2, Floor 1  
Singleton Park  
Swansea

10 February 2021

Miss Alesha Wale  
School of Pharmacy & Pharmaceutical Sciences  
Redwood Building  
King Edward VII Ave  
Cardiff  
CF10 3NB

Dear Miss Alesha Wale

#### Letter of access for research

**REF: 268899 Rec: 19/NW/0598**  
**RE: Unlicensed 'special' medicines**

This letter should be presented to each participating organisation before you commence your research at that site. The participating organisation is: **Swansea Bay University Health Board**.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on **10 February 2021** and ends on **31 July 2021 (current end date of study)** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from **Swansea Bay University Health Board**. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation(s) of their agreement to conduct the research.

The information supplied about your role in research at the organisation(s) has been reviewed and you do not require an honorary research contract with the organisation(s). We are satisfied that such pre-engagement checks as we consider necessary have been carried out. Evidence of checks should be available on request to the organisation(s).

You are considered to be a legal visitor to the organisations premises. You are not entitled to any form of payment or access to other benefits provided by the organisation(s) or this organisation to



Pencadlys BIP Bae Abertawe, Un Porthfa Talbot, Port Talbot, SA12 7BR / Swansea Bay UHB Headquarters, One Talbot Gateway, Port Talbot, SA12 7BR

Bwrdd Iechyd Prifysgol Bae Abertawe yw enw gweithredu Bwrdd Iechyd Lleol Prifysgol Bae Abertawe  
Swansea Bay University Health Board is the operational name of Swansea Bay University Local Health Board

employees and this letter does not give rise to any other relationship between you and the organisation(s), in particular that of an employee.

While undertaking research through the organisation(s) you will remain accountable to your substantive employer but you are required to follow the reasonable instructions of the organisation(s) or those instructions given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the organisation(s) in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with the organisations policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with the organisation(s) in discharging its/their duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 2018. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) do not accept responsibility for damage to or loss of personal property.

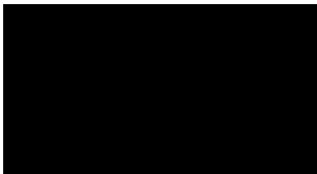
This organisation may revoke this letter and any organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you **MUST** stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 2018. Any breach of the Data Protection Act 2018 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in each participating organisation and the R&D office in this organisation.

Yours sincerely



Research Facilitator  
SBU HB R&D Department



Bwrdd Iechyd Prifysgol  
Cwm Taf Morgannwg  
University Health Board

Your Ref/ eich cyf  
Our ref/ ein cyf:  
Date/ dyddiad:  
Tel/ ffôn:  
Fax/ ffacs:  
Email/ ebost:  
Dept/ adran:

CT/1220/268899  
JG/JLO  
30/03/2021  
01443 444471  
01443 443420

Research & Development Dept

Miss Alesha Wale,  
School of Pharmacy and Pharmaceutical Sciences  
Redwood Building  
King Edward Ave VII  
Cardiff  
CF10 3NB

Dear Miss Wale,

Re: LETTER OF ACCESS FOR RESEARCH

CT/1220/268899	Unlicensed 'special' medicines; improving the patients' experience
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This letter confirms your right of access to conduct research through Cwm Taf Morgannwg University Health Board for the purpose and on the terms and conditions set out below. This right of access commences on 30/03/2020 and ends on 30/06/2021 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Cwm Taf Morgannwg University Health Board has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Cwm Taf Morgannwg University Health Board premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Cwm Taf Morgannwg University Health Board, you will remain accountable to your employer Cardiff University but you are required to follow the reasonable instructions in this NHS organisation or those given on her behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this

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**Return Address:** Research & Development Department, Royal Glamorgan Hospital,  
Llantrisant, Rhondda Cynon Taff, CF72 8XR

Chair/Cadeirydd: Professor Marcus Longley

Chief Executive/Prif Weithredydd: Mrs Allison Williams

Cwm Taf University Health Board is the operational name of Cwm Taf University Local Health Board/Bwrdd Iechyd Prifysgol Cwm Taf yn enw gweithredol Bwrdd Iechyd Lleol Cwm Taf

NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Cwm Taf Morgannwg University Health Board policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Cwm Taf Morgannwg University Health Board in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Cwm Taf Morgannwg University Health Board premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your HEI employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Cwm Taf Morgannwg University Health Board will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours Sincerely



R&D Support Officer



GIG  
CYMRU  
NHS  
WALES

Bwrdd Iechyd  
Addysgu Powys  
Powys Teaching  
Health Board

Gweithrediadau Adnoddau Dynol  
Ward Hafren  
Ychyd Bronllys  
Bronllys, Aberhonddu  
Powys LD3 0LU  
Ffôn: 01874 712589

HR Operations  
Hafren Ward  
Bronllys Hospital  
Bronllys, Brecon  
Powys LD3 0LU  
Phone: 01874 712589

Private and Confidential

30<sup>th</sup> April, 2020

Dear Alesha

### Letter of access for research

We are satisfied that the research activities that you will undertake in this NHS organisation are commensurate with the activities you undertake for your employer. Your employer is fully responsible for ensuring such checks as are necessary have been carried out. Your employer has confirmed in writing to this NHS organisation that the necessary pre-engagement check are in place in accordance with the role you plan to carry out in this organisation. This letter confirms your right of access to conduct research through Powys (teaching) Health Board for the purpose and on the terms and conditions set out below. This right of access commences on 27<sup>th</sup> January, 20 and ends on 27<sup>th</sup> January, 23 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

You are considered to be a legal visitor to Powys (teaching) Health Board premises. You are not entitled to any form of payment or access to other benefits provided by this organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Powys (teaching) Health Board, you will remain accountable to your employer Cardiff University, but you are required to follow the reasonable instructions of your nominated manager in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in

Both Cardiff (De)  
Neuadd Brachynig, Cardiff Cambrian,  
Aberhonddu, Powys LD3 7HR  
Ffôn: 01874 711681

Corporate Hub (South)  
Neuadd Brachynig, Cambrian Way,  
Brecon, Powys LD3 7HR  
Tel: 01874 711681

Ychyd Bronllys (De)  
Ychyd Bronllys, Powys LD3 0LU  
Ychyd Bronllys, Powys



We welcome correspondence in Welsh  
Powys Teaching Health Board is the operational name of  
Powys Teaching Local Health Board

connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Powys (teaching) Health Board policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Powys (teaching) Health Board in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Powys (teaching) Health Board premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

Powys (teaching) Health Board will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the NHS organisation that employs you through its normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely



**Assistant Director of Workforce and Organisational Development  
(Operations)**

CC Bethan Davies, Medicines Management, Bronllys Hospital.

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**Partner Organisations:**

Health Research Authority, England  
 NHS Research Scotland  
 HSC Research & Development, Public Health Agency, Northern Ireland

NIHR Clinical Research Network, England  
 NISCHR Permissions Co-ordinating Unit, Wales

**Notification of Non-Substantial/Minor Amendments(s) for NHS Studies**

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.

**If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.**

**Instructions for using this template**

- For guidance on amendments refer to <http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/>
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at <http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/>. If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

**1. Study Information**

<b>Full title of study:</b>	Unlicensed 'special' medicines; improving the patients' experience.
<b>IRAS Project ID:</b>	268899
<b>Sponsor Amendment Notification number:</b>	NSA01
<b>Sponsor Amendment Notification date:</b>	07/01/20
<b>Details of Chief Investigator:</b>	
Name (first name and surname)	Dr Efi Mantzourani
Address:	Redwood Building King Edward VII Avenue Cardiff
Postcode:	CF10 3NB
Contact telephone number:	02920870452
Email address:	[REDACTED]
<b>Details of Lead Sponsor:</b>	
Name:	Helen Falconer
Contact email address:	[REDACTED]
<b>Details of Lead Nation:</b>	
Name of lead nation <i>delete as appropriate</i>	Wales
If England led is the study going through CSP? <i>delete as appropriate</i>	N/A
<b>Name of lead R&amp;D office:</b>	Aneurin Bevan University Health Board

**Partner Organisations:**

Health Research Authority, England

NIHR Clinical Research Network, England

NHS Research Scotland

NISCHR Permissions Co-ordinating Unit, Wales

HSC Research &amp; Development, Public Health Agency, Northern Ireland

**2. Summary of amendment(s)**

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.

If you need to notify a **Substantial Amendment** to your study then you **MUST** use the appropriate **Substantial Amendment** form in IRAS.

No.	Brief description of amendment <i>(please enter each separate amendment in a new row)</i>	Amendment applies to <i>(delete/ list as appropriate)</i>		List relevant supporting document(s), including version numbers <i>(please ensure all referenced supporting documents are submitted with this form)</i>		R&D category of amendment <i>(category A, B, C) For office use only</i>
		Nation	Sites	Document	Version	
1	Contact number of the study co-ordinator has changed and been updated on the study documents	Wales	All sites or list affected sites	Social media advert	2	
				Cover letter for primary care gatekeepers (Study 1)	3	
				Cover letter for secondary care gatekeepers (Study 1)	3	
				Participant information booklet	4	
				Participant information sheet (Study 1)	4	
				Cover letter for primary care gatekeepers (Study 2)	3	
				Cover letter for secondary care gatekeepers (Study 2)	2	
				Invitation to participate (Study 2)	2	
				Participant information sheet (Study 2)	4	
2						
3						
4						
5						

[Add further rows as required]

**Partner Organisations:**

Health Research Authority, England

NHS Research Scotland

HSC Research & Development, Public Health Agency, Northern Ireland

NIHR Clinical Research Network, England

NISCHR Permissions Co-ordinating Unit, Wales

**3. Declaration(s)**

**Declaration by Chief Investigator**

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: .....

Print name: .....

Date: .....

.....06/01/2020.....

**Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)**

*The sponsor of an approved study is responsible for all amendments made during its conduct.*

*The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.*

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: .....

Print name: Helen Falconer

Post: Research Governance Officer

Organisation: Cardiff University

Date: 07/01/2020

**Partner Organisations:**

Health Research Authority, England

NHS Research Scotland

HSC Research &amp; Development, Public Health Agency, Northern Ireland

NIHR Clinical Research Network, England

NISCHR Permissions Co-ordinating Unit, Wales

**Notification of Non-Substantial/Minor Amendments(s) for NHS Studies**

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.

**If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.**

**Instructions for using this template**

- For guidance on amendments refer to <http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/>
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at <http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/>. If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

**1. Study Information**

<b>Full title of study:</b>	Unlicensed 'special' medicines; improving the patients' experience.
<b>IRAS Project ID:</b>	268899
<b>Sponsor Amendment Notification number:</b>	NSA02
<b>Sponsor Amendment Notification date:</b>	17.02.20
<b>Details of Chief Investigator:</b>	
Name [first name and surname]	Dr Efi Mantzourani
Address:	Redwood Building King Edward VII Avenue Cardiff
Postcode:	CF10 3NB
Contact telephone number:	02920870452
Email address:	[REDACTED]
<b>Details of Lead Sponsor:</b>	
Name:	Helen Falconer
Contact email address:	[REDACTED]
<b>Details of Lead Nation:</b>	
Name of lead nation <i>delete as appropriate</i>	Wales
If England led is the study going through CSP? <i>delete as appropriate</i>	N/A
<b>Name of lead R&amp;D office:</b>	Aneurin Bevan University Health Board

**Partner Organisations:**

Health Research Authority, England

NHS Research Scotland

HSC Research & Development, Public Health Agency, Northern Ireland

NIHR Clinical Research Network, England

NISCHR Permissions Co-ordinating Unit, Wales

**Partner Organisations:**

Health Research Authority, England

NIHR Clinical Research Network, England

NHS Research Scotland

NISCHR Permissions Co-ordinating Unit, Wales

HSC Research &amp; Development, Public Health Agency, Northern Ireland

**2. Summary of amendment(s)**

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.

**If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.**

No.	Brief description of amendment <i>(please enter each separate amendment in a new row)</i>	Amendment applies to <i>(delete/ list as appropriate)</i>		List relevant supporting document(s), including version numbers <i>(please ensure all referenced supporting documents are submitted with this form)</i>		R&D category of amendment <i>(category A, B, C) For office use only</i>
		Nation	Sites	Document	Version	
1	Version number of the participant information sheets referenced in consent forms were updated.	Wales	All sites or list affected sites	Consent form S1 Consent form S2	V3 V3	
2						
3						
4						
5						

[Add further rows as required]

**Partner Organisations:**

Health Research Authority, England

NHS Research Scotland

HSC Research & Development, Public Health Agency, Northern Ireland

NIHR Clinical Research Network, England

NISCHR Permissions Co-ordinating Unit, Wales

**3. Declaration(s)**

**Declaration by Chief Investigator**

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: .....

Print name: .....

Date: ..... 13/02/2020 .....

**Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)**

*The sponsor of an approved study is responsible for all amendments made during its conduct.*

*The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.*

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: .....

Print name: Helen Falconer

Post: Research Governance Officer

Organisation: Cardiff University

Date: 17.02.20

## Amendment Tool

v1.2.11 Jun 2020

For office use

QC: No

## Section 1: Project Information

Short project title*:	Unlicensed 'special' medicines			
IRAS project ID* (or REC reference if no IRAS project ID is available):	268899			
Sponsor amendment reference number*:	NonSubAmend03			
Sponsor amendment date* (enter as DD/MM/YY):	09 July 2020			
Summary of amendment including justification*:	Due to the COVID-19 restrictions and challenges with obtaining post and written consent, we will be offering additional options for participants. We will be using the document attached, printing it off and inserting it into the patient information booklets to encourage responses through email or phone, rather than through the post. As suggested by the HRA guidance and the joint statement on seeking consent by electronic methods ( <a href="https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/">https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/</a> ) (file:///C:/Users/Ajitt/Downloads/hra-mhra-econsent-statement-sept-18.pdf) We will now be seeking e-consent, this will include no change to the text on the consent form and can be received again through email or phone.			
Project type:	<input checked="" type="radio"/> Specific study <input type="radio"/> Research tissue bank <input type="radio"/> Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	<input checked="" type="radio"/> Yes <input type="radio"/> No			
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable?:	<input checked="" type="radio"/> NHS/HSC REC <input type="radio"/> Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a modified amendment?	<input type="radio"/> Yes <input checked="" type="radio"/> No			
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve access to confidential patient information without consent OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve prisoners OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve NHS/HSC organisations prior to this amendment?:	<input checked="" type="radio"/> Yes		<input type="radio"/> No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Which nations had participating NHS/HSC organisations prior to this amendment?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Which nations will have participating NHS/HSC organisations after this amendment?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## Section 2: Summary of change(s)

**Please note:** Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the amendment tool as three separate changes. A list of all possible changes is available on the "Glossary of Changes" tab. To add another change, tick the "Add another change" box.

Change 1	
Area of change (select)*:	Study Documents



Specific change (select - only available when area of change is selected first)*:	Other minor document change that can be implemented within existing resource in place at participating organisations - Please specify in the free text below			
Further information (free text):	Participants will be asked to contact the researcher directly if interested in taking part and given the option to send a photo of the completed survey through email or phone. At this point participants will be supplied with a copy of the consent form, through post or email and asked to sign this physically taking a picture once completed, or electronically, and to send to the researcher through email or phone. The text on the consent form will not be edited and the study overall poses minimal risk to participants, as such we believe following the guidance linked to above, that e-consent should be adequate and that the changes suggested will be considered a non-substantial amendment.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Will all participating NHS/HSC organisations be affected by this change, or only some?*	<input checked="" type="radio"/> All		<input type="radio"/> Some	
Add another change: <input type="checkbox"/>				

**Section 3: Declaration(s) and lock for submission**

**Declaration by the Sponsor or authorised delegate**

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name (first name and surname)\*: Helen Falconer

Email address\*: [REDACTED]

**Lock for submission**

**Please note:** This button will only become available when all mandatory (\*) fields have been completed. When the button is available, clicking it will generate a PDF copy of the completed amendment tool that can be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

**Lock for submission**

After locking the tool, refer to the "Submission Guidance" tab for further information about the next steps for the amendment.

**Section 4: Review bodies for the amendment**

**Please note:** This section is for information only. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies														Category:				
	UK wide:				England and Wales:				Scotland:			Northern Ireland:							
	REC	Complaint Authority MRPRA - Medicines	Complaint Authority MRPRA - Devices	ARSAAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HAPPS	HRA and HCRW Approval	REC (NWA)	pgjpp	SPS (PAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	
Change 1:						(Y)				(Y)									C
<b>Overall reviews for the amendment:</b>																			
Full review:						N				N									
Notification only:						Y				Y									
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

<b>Amendment Tool</b> v1.2.11 Jun 2020	For office use QC: No
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**Section 1: Project Information**

Short project title*:	Unlicensed 'special' medicines; improving the patients experience			
IRAS project ID* (or REC reference if no IRAS project ID is available):	268899			
Sponsor amendment reference number*:	NonSubAmend04			
Sponsor amendment date* (enter as DD/MM/YY):	30 August 2020			
Summary of amendment including justification*:	For Cardiff and Vale Health Board, we will identify three local collaborators that will help with local recruitment within secondary care settings. (Paediatrics, Dermatology and Gastroenterology departments)			
Project type:	<input checked="" type="radio"/> Specific study <input type="radio"/> Research tissue bank <input type="radio"/> Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	<input checked="" type="radio"/> Yes		<input type="radio"/> No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable?:	<input checked="" type="radio"/> NHS/HSC REC <input type="radio"/> Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a modified amendment?	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve access to confidential patient information without consent OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve prisoners OR does the amendment introduce this?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve NHS/HSC organisations prior to this amendment?:	<input checked="" type="radio"/> Yes		<input type="radio"/> No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Which nations had participating NHS/HSC organisations prior to this amendment?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Which nations will have participating NHS/HSC organisations after this amendment?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Section 2: Summary of change(s)**

**Please note:** Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the amendment tool as three separate changes. A list of all possible changes is available on the "Glossary of Changes" tab. To add another change, tick the "Add another change" box.

Change 1	
Area of change (select)*:	Participating Organisations

Specific change (select - only available when area of change is selected first):	PICs - Addition of Participant Identification Centres for the first time, or a change to activities undertaken by existing PICs			
Further information (free text):	It has been agreed with Cardiff and Vale University Health Board that selected local collaborators are to be identified for the study. Cardiff and Vale UHB will act as a PIC.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Will all participating NHS/HSC organisations be affected by this change, or only some?:	<input type="radio"/> All		<input checked="" type="radio"/> Some	
Add another change: <input type="checkbox"/>				

**Section 3: Declaration(s) and lock for submission**

**Declaration by the Sponsor or authorised delegate**

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name (first name and surname)\*: Helen Falconer

Email address\*: [REDACTED]

**Lock for submission**

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Lock for submission

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**Section 4: Review bodies for the amendment**

**Please note:** This section is for information only. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies														Category:				
	UK wide:				England and Wales:				Scotland:			Northern Ireland:							
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	APRSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPS	HRA and HCRW Approval	REC (AWA)	PSPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Pharms	National coordinating function	
Change 1:						Y				Y									B
Overall reviews for the amendment:																			
Full review:						Y				Y									
Notification only:						N				N									
Overall amendment type:	Non-substantial																		
Overall Category:	B																		

Amendment Tool		For office use		
v1.4 30 Nov 2020		QC: No		
<b>Section 1: Project information</b>				
Short project title*:	Unlicensed 'special' medicines			
IRAS project ID* (or REC reference if no IRAS project ID is available):	268899			
Sponsor amendment reference number*:	NSA05			
Sponsor amendment date* (enter as DD/MM/YY):	14 January 2021			
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	Project to be extended due to delays experienced as a result of the COVID-19 virus.			
Project type (select):	<input checked="" type="radio"/> Specific study <input type="radio"/> Research tissue bank <input type="radio"/> Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment*:	<input checked="" type="radio"/> Yes <input type="radio"/> No			
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	<input checked="" type="radio"/> NHS/HSC REC <input type="radio"/> Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a <b>modified amendment</b> (i.e. a substantial amendment previously given an unfavourable opinion)?	<input type="radio"/> Yes <input checked="" type="radio"/> No			
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based*:	England	Wales	Scotland	Northern Ireland
	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve adults lacking capacity OR does the amendment introduce this*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve prisoners OR does the amendment introduce this*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Did the study involve NHS/HSC organisations prior to this amendment*:	<input checked="" type="radio"/> Yes		<input type="radio"/> No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them*:	<input type="radio"/> Yes		<input checked="" type="radio"/> No	
Lead nation for the study:	England	Wales	Scotland	Northern Ireland
	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
Which nations had participating NHS/HSC organisations prior to this amendment*:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Which nations will have participating NHS/HSC organisations after this amendment*:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Section 2: Summary of change(s)**

**Please note:** Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the amendment tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, tick the "Add another change" box.

Change 1	
Area of change (select)*:	Study Design

Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below			
Further information (free text - note that this field will adapt to the amount of text entered):	Recruitment and data collection to be extended to June 30th 2021, project to be completed and ended by July 31st 2021			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Will all participating NHS/HSC organisations be affected by this change, or only some? (please note that this answer may affect the categorisation for the change):	* All		○ Some	

Add another change:

**Section 3: Declaration(s) and lock for submission**

**Declaration by the Sponsor or authorised delegate**

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name (first name and surname)*:	Chris Shaw
Email address*:	[REDACTED]

**Lock for submission**

**Please note:** This button will only become available when all mandatory (\*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

**Lock for submission**

After locking the tool, [proceed to submit the amendment online](#). The "Submission Guidance" tab provides further information about the next steps for the amendment.

**Section 4: Review bodies for the amendment**

**Please note:** This section is for information only. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies														Category:				
	UK wide:					England and Wales:				Scotland:			Northern Ireland:						
	REC	Compliant Authority MRPRA - Medicines	Compliant Authority MRPRA - Devices	ARSAAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPSS	HRA and HCRW Approval	REC (AWRA)	PEPP	SPS (RAEC)	National coordinating function		HSC REC	HSC Data Guardians	Prisons	National coordinating function
Change 1:						(Y)					(Y)								C
Overall reviews for the amendment:																			
Full review:						N					N								
Notification only:						Y					Y								
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

## **Appendix 9. Survey tool created for community pharmacy staff**

**Survey for community pharmacy staff.**

**Community pharmacy staff took part in interviews to discuss their views and experiences around accessing and supplying unlicensed 'special' medicines.**

**We would love to hear your views and experiences!**

**This should take approx. 15-20 mins to complete.**

## 1. About you

**A. What is your current job role?**

Community pharmacist [  ] Community pharmacy technician [  ]

**B. How old are you?** \_\_\_\_\_

**C. How long have you been in this position?**

[  ] Years [  ] Months

**D. Do you have any other experience in a different healthcare setting? (If yes please give job roles and numbers of years in these roles).**

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**E. Are you currently working at a chain or independent pharmacy?**

[  ] Independent (1-5 sites) [  ] Small multiple (6-99 sites) [  ] Large multiple (100+ sites)

**F. How many specials are dispensed from your pharmacy on average per month?**

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**G. How would you define an unlicensed 'special' medicine?**

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**H. How do you feel about your role of responsibility in supplying unlicensed 'special' medicines to the public?**

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## 2. Receiving and processing prescriptions for unlicensed 'special' medicines

**A. What information do you receive with prescriptions for unlicensed 'special' medicines?**

**From the GP–**

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**From the Hospital –**

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**B. Are you given details of the supplier used for the prescribed unlicensed ‘special’ medicine by the discharging hospital?**

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**C. What type of information would you like to receive with prescriptions for unlicensed ‘special’ medicines? Or what has been the most helpful type of information received?**

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**D. What considerations do you make before deciding to supply an unlicensed ‘special’ medicine?**

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**E. Do your SOP’s recommend or require any checks that must be made before accessing and supplying a prescription for an unlicensed ‘special’ medicine? If yes, please provide details**

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**F. Have you ever experienced receiving a prescription for an unlicensed ‘special’ medicine where an alternative licensed medicine was available and suitable for the patient? If yes, please explain how this was determined, what was done and how this situation was corrected.**

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**G. Please state your agreement with the following sentences (please tick).**

**1. Information received from the hospital or GP with prescriptions for unlicensed ‘special’ medicine are consistent for different unlicensed ‘special’ medicines.**

Strongly Disagree	Disagree	Slightly Disagree	Neither Agree nor Disagree	Slightly Agree	Agree	Strongly Agree

**2. I am always provided with enough information with prescriptions to feel I can make clinically informed decisions about supplying unlicensed ‘special’ medicines.**



Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**3. I contact the original prescriber for further information before deciding to continue to supply a new prescription for an unlicensed 'special' medicine.**

Strongly Disagree	Disagree	Slightly Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**4. I will do some research on any unfamiliar or unusual unlicensed 'special' medicines prescribed before deciding to supply the medicine.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**5. I discuss the patients' need with the patient before deciding to continue a prescription for an unlicensed 'special' medicine.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

### 3. Interaction with patients

**A. Have conversations with patients ever provided enough information to determine the unlicensed 'special' medicine prescribed was not the most suitable treatment? If yes, please provide details.**

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**B. Have you experienced patients refusing to take unlicensed 'special' medicines because they are unlicensed? If yes, please provide details.**

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**C. Please state your agreement with the following sentences (please tick).**

**1. Patients are always informed their medicine is unlicensed prior to bringing a prescription into the pharmacy.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**2. Patients understand the differences in process and often timelines when first accessing their unlicensed 'special' medicine.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**3. I usually discuss with the patient that there medicine is unlicensed and the timelines involved.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**4. Patients are expected to inform the pharmacy in advance of when further supplies are needed.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**5. Patients usually are not concerned about their medicine being classed as unlicensed.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**D. Please provide any extra detail about the interactions you have with patients when they first bring in a prescription for and unlicensed 'special' medicines, or views that patients have shared with you about the use of unlicensed 'special' medicines**

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## 4. Ordering and supplying unlicensed 'special' medicines

**A. What supplier(s) do you use to order unlicensed 'special' medicines?**

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**B. Do you have an online ordering system in place for unlicensed 'special' medicines? If yes, how does this compare to other methods used in the past to order unlicensed 'special' medicines? If no, please provide details of your current process.**

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**C. Do you use a fax machine within the pharmacy?**

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**D. Do you order unlicensed 'special' medicines on a named patient basis?**

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**E. Is the paperwork received with unlicensed 'special' medicines consistent across suppliers?**

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**F. Is the associated paperwork (i.e certificate of conformity/analysis) always received at the same time as the unlicensed 'special' medicine is received?**

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**G. Have you ever experienced delays in receiving unlicensed 'special' medicines from suppliers? If yes, please provide some details (medicine delayed, reason for delay, length of delay, outcome of delay on treatment).**

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**H. Have you ever had to import an unlicensed 'special' medicine? If yes, please provide details (medicine imported, timelines involved, cost, process).**

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**I. Are there any additional records kept about unlicensed 'special' medicines supplied?**

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**J. How do you feel about the costs of unlicensed ‘special’ medicines from suppliers?**

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**K. Have you ever experienced a GP refusing to continue a prescription for unlicensed ‘special’ medicines? If yes, please provide details (medicines refused, reasons for refusal, how you were informed, impact on patient care).**

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## **5. Getting reimbursed**

**A. Have you ever had any issues getting reimbursed for unlicensed ‘special’ medicines? If yes, please provide details.**

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**B. Have you ever had to refuse to supply an unlicensed ‘special’ medicine due to the cost of the medicine prescribed? If yes, please provide details.**

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**C. Roughly what percentage of the unlicensed ‘special’ medicines you supply are listed on section VIIB of the drug tariff?**

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**D. How long does the process of reimbursement usually take for unlicensed ‘special’ medicines?**

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## **6. Safety and efficacy**

**A. Have you ever had to report any adverse drug reactions for patients as a result of receiving an unlicensed ‘special’ medicine? If yes, please provide details**

**B. Have you ever experienced an unlicensed 'special' medicine not being effective for the patient? If so, How was this handled?**

**C. Please state your agreement with the following sentences (please tick).**

**1. I am confident that prescriptions for unlicensed 'special' medicines initiated in secondary care have been assessed as the most suitable treatment for the patients' needs.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**2. I am confident that prescriptions for unlicensed 'special' medicines initiated in primary care have been assessed as the most suitable treatment for the patients' needs.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**3. I am confident that manufacturers have produced unlicensed 'special' medicines to a certain standard that has been found to be safe.**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**4. I am confident in the safety of unlicensed 'special' medicines**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

**5. I am confident in the efficacy of unlicensed 'special' medicines**

Strongly Disagree	Disagree	Slightly Disagree	Neither agree not Disagree	Slightly Agree	Agree	Strongly Agree

## **7. Improvements or areas to target.**

**Are there any key areas that you think could be targeted to improve the process of receiving prescriptions for, accessing, or supplying unlicensed 'special' medicines?**

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**Thank you for taking part in the survey!**