

**Patient and public  
involvement in the benefit-  
risk assessment of medicines:  
developing a semi-  
quantitative framework to  
incorporate patient views as  
key criteria in decision-  
making**

A thesis submitted in accordance with the  
conditions governing candidates for the degree of  
Philosophiae Doctor in Cardiff University

by


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## DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD.

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## **Abstract**

During a drug's lifecycle, evidence must demonstrate that the benefits of the product continue to outweigh the risks. Benefit-risk (B-R) assessment is a vital stage of the drug approval process and is an important task for regulators. Involving patients in B-R assessment is a recent development. Patients may view benefits and risks very differently when compared with the views of pharmaceutical companies or regulatory assessors. The aim of this research was to investigate this topic to ultimately propose a framework for involving patients in this process. The research strategy involved three phases. In phase I, a survey was submitted to (1) pharmaceutical companies and regulatory agencies and (2) patient advocacy groups across Europe, to obtain their opinions on involving patients in B-R assessment. Phase I of the research identified several challenges, including: how to ensure adequate representation of patients and a lack of an established method. It was also identified that to date, only patient advocacy groups were directly involved in B-R assessment discussions. However, some companies were developing initiatives to involve patients. Based on these findings, phase II was implemented, where individuals from regulatory agencies, pharmaceutical companies and patient advocacy groups participated in semi-structured interviews to identify themes around patient involvement and to establish rich data around the current challenges. This data was used to inform the development of a novel framework, one element of which was tested in phase III of the research; where qualitative focus groups were conducted with patients. The framework proposed from this research, therefore, involves qualitative focus groups, enabling patients to provide insight into their disease and treatment. The information obtained, when presented alongside quantitative preference elicitation data, may then be used to contribute to B-R discussions by regulators, to ultimately support their decision-making.

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## **Glossary of terms and abbreviations**

### **Adverse Event (AE)**

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, which does not necessarily have a causal relationship with this treatment (Directive 2001/20/EC)

### **Adverse Drug Reaction (ADR)**

All untoward and unintended responses to a medicinal product at any dose administered (Directive 2001/20/EC).

### **Benefit**

In the context of this thesis, defined as ‘something that promotes wellbeing’ or ‘a potential favourable effect of a drug on the current state of health’ (Mussen, Salek and Walker, 2009).

### **Benefit-risk (B-R) assessment**

The assessment made after understanding the various benefits of a treatment and comparing them against the associated safety issues (Sashegyi, Felli and Noel, 2014).

### **Benefit-risk balance**

A comparison of the benefits of a treatment against the associated safety issues (Sashegyi, Felli and Noel, 2014).

### **Benefit-Risk Action Team (BRAT)**

‘BRAT standardises and supports the decision and communication of a BR assessment between pharmaceutical companies and the regulators through a 6-step process: define decision context, identify outcomes, identify data sources, customise framework, assess outcome importance, and display and interpret key BR metrics’ (Noel *et al.*, 2012; IMI PROTECT, 2018).

### **Decision-making**

In the context of this thesis, 'decision-making' refers to decisions made by regulatory agencies which 'pertains to the approval of new medicines' (Mussen, Salek and Walker, 2009).

### **European Medicines Agency (EMA)**

'A decentralised agency of the European Union (EU), located in London, and soon to move to Amsterdam once the UK leaves the EU. It began operating in 1995. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU' (EMA, 2018).

### **European Union (EU)**

'A political and economic union of twenty-eight Member States; located primarily in Europe' (EU, 2018).

### **European Patients' Academy on Therapeutic Innovation (EUPATI)**

An EU funded initiative which 'aimed to trigger a major rethink in the way patients and the public understand the medicines development process and their own involvement therein' (EUPATI, 2018).

### **Food and Drug Administration (FDA)**

The United States agency responsible for 'protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation' (FDA, 2018).

### **Good Clinical Practice (GCP)**

'An international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects' (EMA, 2002, p. 7)



### **Guy's and St Thomas' NHS Foundation Trust (GSTT)**

A South London National Health Service Trust composed of Guy's Hospital at London Bridge and St Thomas' Hospital, Westminster, where this research was undertaken.

### **IMI Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT)**

'A collaborative European project that comprises a programme to address limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance' coordinated by the EMA and GlaxoSmithKline (GSK) (IMI PROTECT, 2018a).

### **INVOLVE**

Established in 1996 and funded by, the National Institute for Health Research, 'INVOLVE is an initiative to support active public involvement in NHS, public health and social care research. It is one of the few government funded programmes of its kind in the world' (INVOLVE, 2018).

### **Medicines and Healthcare products Regulatory Agency (MHRA)**

An executive agency of the UK Department of Health 'responsible for ensuring that medicines and medical devices work and are acceptably safe' (MHRA, 2012) and the UK Competent Authority for oversight of clinical trials that fall within the scope of The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments.

### **National Health Service (NHS)**

The UK public sector health care service, free at the point of care and funded by national insurance and taxes.

### **Patient and Public Involvement (PPI)**

In the context of this thesis, PPI refers to the involvement of lay people in benefit-risk assessment. Their involvement is active participation; being carried out 'with' or 'by' members of the public rather than 'to,' 'about' or 'for' them' (INVOLVE, 2018).

### **Patient Reported Outcome Measures (PROMs)**

'A set of standardised measures used to capture patient reported outcomes, including symptom status, physical function, mental health, social function, and wellbeing' (Nelson, *et al.*, 2015).

### **Pharmacovigilance**

'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems' (WHO, 2018).

### **PREFER**

'PREFER will establish recommendations to support development of guidelines for industry, Regulatory Authorities and HTA bodies on how and when to include patient perspectives on benefits and risks of medicinal products' (PREFER, 2018).

### **PrOACT-URL Framework**

PrOACT-URL is the EMA's generic decision-making guide with eight steps: Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions. the EMA's Benefit-Risk Project adapted PrOACT-URL is focussed on the decision-making of medicines (IMI PROTECT, 2018b).

### **Qualitative research**

'An approach for exploring and understanding the meaning individuals or groups ascribe to a social or human problem. The process of research involves emerging questions and procedures, data typically collected in the

participant's setting, data analysis inductively building from particulars to general themes, and the researcher making interpretations of the meaning of the data' (Creswell, 2014).

### **Quantitative research**

'An approach for testing objective theories by examining the relationship among variables. These variables can be measured, typically on instruments, so that numbered data can be analysed using statistical procedures' (Creswell, 2014).

### **Research Ethics Committee (REC)**

An independent committee comprised of medical professionals and lay members who must ensure the protection of the rights, safety and well-being of human subjects by reviewing and providing favourable ethical opinion on a proposed trial, often called 'REC approval' (Directive 2001/20/EC).

### **Research and Development (R&D)**

The department within a National Health Service hospital responsible for reviewing all research projects to be conducted within the organisation and ultimately giving research management approval; often called 'R&D approval'.

### **Risk**

In the context of this thesis, the 'possibility of loss or injury, peril' (Mussen, Salek and Walker, 2009).

### **Semi-quantitative research**

This term, used regularly by regulatory agencies and pharmaceutical companies, refers to a 'mixed-methods' approach. 'This approach to inquiry involves collecting both quantitative and qualitative data, integrating the two forms of data, and using distinct designs that may involve philosophical assumptions and theoretical frameworks' (Creswell, 2014).

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# **Chapter I: General introduction**

## **Introduction**

When considering those personnel involved in developing novel drugs and compounds, a list of stakeholders comes to mind. They include pharmaceutical companies, who develop and manufacture the molecule. These companies invest large amounts of money to enable the product to reach a level of development suitable to move to testing; in clinical trials. There are clinical teams of doctors, nurses, trial managers and study coordinators, undertaking clinical trials within hospitals and clinical research organisations. In addition, there are the regulatory agencies, responsible for assessing the drug's efficacy and safety based on clinical trial data often collected over many years, both before and after licensing. One of the most important stakeholders, however, may be considered last when considering regulatory drug development: i.e., the patient. Of course, all stakeholders would agree that 'patients come first, ahead of science and society' (ICH GCP, 1996, p. 15). Patients' rights, safety and well-being are paramount under the international standard of ICH Good Clinical Practice, to which all clinical trials must adhere to. It goes without saying that, clinical researchers, pharmaceutical companies and regulatory agencies, inevitably prioritise patients when a clinical trial of a new compound is set-up and developed.

Even so, apart from those examples where patient reported outcome measures (PROMs) are incorporated into a clinical trial protocol, how often are patients asked exactly what they think of the study they are taking part in? Are they questioned about the drug they are taking, in the context of what it actually means to them on a personal level? They will have undoubtedly been questioned about the most obvious effects on their daily living, since taking the drug, as well as any side effects they may have experienced. To reiterate the point, this matter is not merely about patient safety or the list of adverse events a patient may or may not have experienced over the previous month. It is argued that the general questions asked of patients participating in clinical trials do not adequately take into consideration what patients actually think about the trial, or their treatment.

As patient and public involvement becomes central to policy development across a range of industries, the general trend is that it is now time to include patients in all aspects of a clinical trial. This encompasses trial design through to the conduct and subsequent data analysis and hopefully, if the study is positive, drug licencing. Surely, in today's world of democratic devolution it is essential that patients are also included in regulatory decision-making regarding new drugs. It would be predictably advantageous that patients should have a voice on this topic and as such, they should contribute to decisions on drug licencing.

Nevertheless, how do we know that including patients in this vital process will enhance an already clearly defined and robust process? Can we be sure that patients are not being exposed to greater risk by involving those patients who may lack the experience and understanding necessary in essential decision-making? These are questions that must be posed, and it is for these reasons that further research into the topic of patient inclusion in benefit-risk assessment is essential. The crucial question is, however, should patients be involved in this process at all?

It is clear that involving patients directly in benefit-risk assessment during drug development is becoming increasingly important. It has been widely recognised that patients may view benefits and risks differently when compared with the views of pharmaceutical company representatives or regulatory assessors (Mussen, Salek and Walker, 2009). Several regulators and pharmaceutical companies have already implemented strategies to engage patients directly in their benefit-risk assessment activities, including the Food and Drug Administration in the US and the European Medicines Agency (FDA, 2013; EMA, 2014). The involvement of patient advocacy groups and patient representatives has also been shown to be valuable not only in benefit-risk considerations, especially from the standpoint of risk tolerability, but it has also aided the decision-making process (Bernabe *et al.*, 2014).



The inclusion of patients has particular relevance to the risk management plan of a clinical study, which is an important requirement of the new Clinical Trials Regulation (EU) No 536/2014 (European Commission, 2014). Indeed, the level of risk that an individual is willing to accept may be higher or lower than anticipated, depending on the degree of benefit delivered by their medication. This information may inevitably have a useful impact throughout the pre-authorisation phases of clinical development and it is also important subsequent to the drug's authorisation, during post-marketing surveillance.

The question now is not whether patients should be involved, as this is unequivocal, but how they can be incorporated into a benefit-risk assessment framework. Several potential methods have been considered and investigated by the IMI PROTECT consortium (IMI PROTECT, 2015) although a validated method for including patients has not yet been forthcoming.

Quantitative benefit-risk preference-elicitation methods include discrete choice experiments, rating scales, threshold technique, standard gamble and conjoint-analysis (Hauber *et al.* 2013; Hiligsmann *et al.*, 2014). In the context of benefit-risk assessment, these methods could be greatly enhanced when combined with a qualitative element, which would be essential in allowing patients the opportunity to communicate what is most important to them. This tactic can generate significantly richer data than a quantitative approach alone. Some participation has already occurred, via patient advocacy groups, whom, in collaboration with pharmaceutical companies and academia have completed several benefit-risk preference studies (Wolka, *et al.*, 2017).

One proposed 'semi-quantitative' methodology would be to undertake qualitative focus groups enabling patients to provide insight into their disease and treatment. The information obtained, when presented alongside quantitative preference elicitation study data, may then be used to contribute to B-R discussions by regulators, to ultimately support their decision-making. Any method developed would need to be appraised by key stakeholders involved in benefit-risk assessment, including regulators and pharmaceutical companies, to ensure it is fit for purpose. Patient representatives and patient advocacy groups would need to be consulted to confirm that the method proposed was pragmatic and retained patient acceptability. Several challenges would need to be overcome during this process.

Thus, patient identification and selection must be considered to verify that those patients to be included were drawn from a range of backgrounds. In addition, demographic characteristics, disease severity and prognosis would all need to be taken into account, so that the patient groups were as representative as possible. Although challenges remain, further research on this topic presents a genuine opportunity to significantly enhance the current regulatory framework, which ultimately has real potential to benefit patients.

### **Study rationale**

It is clear from recent initiatives that patient-focused drug development will continue to gain in popularity and will be undoubtedly be used more widely. The FDA's project aimed to address how to use the patient perspective not only to inform their decision-making but to also include their views in a benefit-risk assessment process. Mullard (2013) states that once patient opinions have been collected, using a variety of means (from meetings or from surveys), the next challenge is turning this information into a format suitable for inclusion in a structured and meaningful assessment framework (Mullard, 2013; FDA, 2013b).

This area of research received investment over several years (2013-2017, in particular), however, regulatory agencies and pharmaceutical companies are still yet to publish a standard methodology of incorporating patients in a benefit-risk assessment model or framework. Therefore, this thesis addresses this novel area. It is known that involving patients in regulatory decision-making could greatly improve and enhance the benefit-risk assessment process. It is clear from the literature that the existing benefit-risk assessment models have their strengths and weaknesses. These quantitative models could be substantially enhanced by incorporation of a qualitative element obtained directly from the patients themselves.

This research, accomplished over a similar time period to those projects completed by the regulatory agencies of the US and Europe, has produced a distinctive contribution to information in this area of research. It may not however, be the outcome the reader would initially expect. The general consensus published by the FDA and EMA was that patients must be incorporated in the B-R decision-making process. However, the current study has generated findings some of which may well throw doubt on this assumption.

### **Research focus**

It is clear from the literature, which will be described and critically evaluated further in Chapter II, that involving patients in benefit-risk assessment decision-making was a current topic that required further investigation. This is an issue of international importance, though such a sizeable topic cannot be fully addressed by a single PhD thesis. Be that as it may, this research study has unveiled a number of interesting findings which may possibly contribute to this vital topic. The study employed mixed methods; comprising quantitative surveys, and qualitative semi-structured interviews and focus groups; using a grounded theory approach to generate a novel framework.

The reasons for this research approach were twofold. Firstly, current opinion on whether or not patients should be included in benefit-risk assessment decision-making was probed by surveying pharmaceutical companies, regulatory agencies and patient advocacy groups. This was important to not only identify current opinion but to also identify the actual methods already used to include patients in benefit-risk assessment, if any.

Secondly, qualitative semi-structured interviews and focus groups were selected as an appropriate methodology to include patients. With regards to the framework development, a grounded theory approach was deemed most suitable, as it was expected that novel concepts and themes would be important to contribute to fulfilling the study's aim. In order to achieve the overall aim, several individual research objectives were developed, which are summarised on Page 8.

## **Research aim and objectives**

The aim of this research was to propose a semi-quantitative framework for involving patients in the benefit-risk assessment of medicines.

Specifically, the objectives of this research were to:

(1) Survey pharmaceutical companies and regulatory agencies to discover the degree that patients were already included in benefit-risk assessment within their organisation.

(2) Survey patient advocacy groups to discover their current knowledge on the topic of regulatory benefit-risk assessment of medicines.

(3) Using qualitative semi-structured interviews, establish the opinions of representatives from pharmaceutical companies, regulatory agencies and patient advocacy groups, by undertaking thematic analysis of their views and opinions.

(4) Using focus groups to disclose the views of patients, identify the patient's perspective; to include an insight into their condition and their opinions on patient involvement in benefit-risk assessment discussions.

(5) Using a Grounded Theory (GT) approach, describe, analyse and synthesise these data and ultimately propose a semi-quantitative framework for involving patients in the benefit-risk assessment of medicines.

The study was important to highlight issues related to patient involvement in B-R assessment, already described in Chapter I, and this is an important topic globally. By investigating these objectives, it was anticipated that best practice might one day be developed. This would support the ultimate aim that any novel framework could subsequently be communicated to regulators and pharmaceutical companies. Accordingly, this had the potential to improve current processes around involving patients in B-R assessment.

In Chapter II (Review of Literature), an analysis is presented of the previous projects and studies undertaken within this field. Several international projects, described subsequently, have contributed to knowledge within this topic area. They also investigated a number of key challenges around the involvement of patients in B-R assessment. This was essential to understand during the study design phase, as these challenges would inevitably impact this programme of PhD research.

## **Chapter II: Review of literature**

## **Introduction**

This Review of Literature introduces the following topics: B-R assessment as a general topic, the various stakeholders involved, science communication to lay audiences (which also considers risk communication and risk perception) and patient and public involvement in research. The concept of the 'expert patient' will be fully investigated and a detailed analysis of patient involvement in B-R assessment will be reported. Finally, several international projects currently in progress will be presented, all of which have contributed to the topic of patient involvement in B-R assessment.

## **Benefit-risk assessment of medicines**

Before a new medicine is approved for marketing, and throughout the medicinal product's lifecycle, both before and after licensing, data must be available to demonstrate the safety and efficacy of the drug. A detailed assessment is completed using all available pre-clinical and clinical data; to ensure the benefits of the product are carefully balanced against the risks. B-R assessment is a pivotal stage of the drug approval process and is integral to the activities of regulatory agencies (ICH, 2012). 'The assessment of the benefit-risk in the context of a new drug application is a central element of the scientific assessment of a marketing authorisation' (EMA, 2007, p. 2). B-R assessment has even been transposed into law. As an example, in Europe, Article 26 of Directive 2001/83 as amended states that 'a marketing authorisation shall be refused if the benefit-risk balance is not considered to be favourable or if therapeutic efficacy is insufficiently substantiated' (EMA, 2007, p. 3). An example that demonstrates the complexity of B-R analysis is the treatment of severe combined immunodeficiency (SCID) using gene therapy. SCID is a genetic condition where patients are unable to produce certain immune cells, consequently, they are at extreme risk of infection. Unfortunately, this group of patients do not often survive longer than a few years from birth.



The condition has previously been termed ‘the boy in the bubble’ as one patient became famous in the media for having to remain in a sterile environment in order to prevent infection (Hacein-Bey-Abina et al., 2008). Several Phase I clinical trials have been completed to date on a small group of patients in London and Paris. However, there was a high incidence of adverse events that were later defined as suspected unexpected serious adverse reactions (SUSARs). The SUSARs that occurred in four patients involved ‘insertional oncogenesis,’ the incorporation of a cancer-causing gene resulting in leukaemia (Hacein-Bey-Abina *et al.*, 2008).

Based on this information alone, it would be fair to assume that the risk is too great and the treatment should no longer be used. Notwithstanding this, the leukaemia was treatable using chemotherapy and after treatment three of the patients continued to ‘benefit from the gene transfer’ although one patient died (Hacein-Bey-Abina *et al.*, 2008). The risks of the gene therapy were worthwhile in the majority of cases as the patients survived, whereas without the treatment they would have died. Three of the four patients were cured of their genetic condition and continue to do well. However, in the absence of long-term safety data risks still remain.

Although this research was undertaken for clinical care and there was no intention to submit a marketing authorisation, it is still useful in demonstrating the challenges faced by regulators and pharmaceutical companies when assessing treatments for benefit-risk; as it not always straight-forward. As with many orphan drugs and rare treatments, the B-R balance after reviewing all of this information is perhaps obvious. On the other hand, the benefit-risk balance of the majority of treatments is often not so easy to determine.

The benefit-risk assessment process has been an area of focus in recent years and is a field that is changing rapidly. The Council for International Organisations of Medical Sciences (CIOMS) publicly highlighted the issue in 1998 when they released the following statement:

'It is a frustrating aspect of benefit-risk evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data and that might permit straightforward quantitative comparisons of different treatment options, which in turn might aid in decision-making' (CIOMS, 1998, p. 13).

In response to this, the regulatory agencies of the US, Europe and Japan, who had only up to that juncture issued a list of benefit-risk criteria, recognised that guidance on the various methods for benefit-risk analysis was urgently required, yet it was several years before further literature was published on the subject (EMA, 2007). The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency undertook an audit in 2004 examining exactly how the agency completed benefit-risk analysis. The group appraised the currently available models of benefit-risk assessment, which they confirmed could be placed into two groups: 'models used for individual clinical trials, and general models' (EMA, 2007, p. 3).

## **Models for benefit-risk assessment**

### *Quantitative models*

There are a number of different quantitative models used for benefit-risk analysis. Data from clinical trials are analysed and a decision is made based on the outcome. One popular model used for individual clinical trials is the 'Number Needed to Treat/Number Needed to Harm (NNT/NNH)' (EMA, 2007, p. 3). The NNT is the number of patients who need to be treated to obtain a benefit (defined as 'preventing one additional adverse outcome') whereas 'NNH is the number of patients needed to be treated to identify one adverse treatment related outcome' (EMA, 2007, p. 3). Although this model is simple to use, the CHMP report states that 'the method has essentially been adapted for one clinical trial with binary endpoints. It is unclear how it would account for multiple benefit-risk variables and multiple adverse events of different seriousness' (EMA, 2007, p. 4).

The general models include 'the Principle of three' and the 'Transparent Uniform Risk Benefit Overview (TURBO)' models. The benefit-risk assessment at the time of licensing a novel drug is almost always based on data from a limited number of patients and therefore the benefit-risk assessment process is continuous and ongoing (ICH, 2012). 'In assessing the altered benefit/risk ratio of drugs which appear to be causing clinical toxicity, spontaneous reporting schemes, such as the Yellow Card System in the UK, play a crucial part' (Mann, 2007, p. 705). As accumulating data is collected post-marketing, the status of a drug's marketing authorisation may change depending on the acquisition of additional safety data, to ensure that the benefits continue to outweigh the risks. These general models were therefore developed for the reassessment of marketed medicines in the event that new safety issues arise (EMA, 2007).

The 'principle of three' is a model 'based around the concept of seriousness, duration, and incidence as related to disease indication' (EMA, 2007, p. 4). A grading system is used with each parameter being rated as low, medium or high. This method is based on 'visible weighting of the scores for the level of improvement produced by the medicine against the scores for the adverse effects criteria' (EMA, 2007, p. 4). The TURBO model conversely, is a 'quantitative and graphical approach to benefit-risk analysis' (EMA, 2007, p. 4). The model 'tries to quantify the benefit and risks of a medicine in a given indication and then both factors are displayed in a TURBO diagram' (EMA, 2007, p. 4).

There are several limitations to both these types of general model, in that many of the criteria used are not well defined. In addition, the scores that are used in the analysis are also not defined in comparison to the criteria; opening them up to subjective differences when different assessors undertake the assessment. Both models were developed for medicines that had already been marketed and had not been validated for the B-R analysis of novel medicines (EMA, 2007).

The multi criteria decision analysis (MCDA) model 'uses an algorithm that combines value judgements along multiple dimensions' (EMA, 2007, p. 4). 'Decision-analysis' is widely used throughout the world of business as well as within various government departments. This decision-making is used in areas such as managing R&D programmes, for new product launches, or responding to environmental risks (EMA, 2007, p. 4). This MCDA model involves developing a list of relevant benefit and risk criteria that can then be used for determining a benefit-risk profile. These criteria are then organised depending on their importance in the overall decision (termed 'weighting'). Each criterion can be scored, weighted and then a calculation can be undertaken using computer software (EMA, 2007, p. 5). This model has been accepted by a number of organisations as best practice.

This particular quantitative model is useful in that it can be used to evaluate benefit-risk between different treatment arms, against placebo or an active control as it uses numerical values and scoring to make the decisions. On the other hand, 'there is a danger that decision over relies on the numerical outcome analysis of the model' (EMA, 2007, p. 5). In addition, developing this model for a single drug is time consuming due to the list of criteria that need to be developed. However, it does allow for the subjective discussion between clinicians who act as assessors; which can be a useful training tool (EMA, 2007, p. 5).

In their book, 'Benefit-Risk Appraisal of Medicines, A systematic approach to decision-making' published in 2009, Mussen, Salek and Walker presented a detailed case for the reasons why a standardised model for benefit-risk assessment of medicines is required. Previously there was no standardised model for such an assessment and therefore regulatory agencies and industry conducted the benefit-risk assessment process using a variety of models as described previously (Mussen, Salek and Walker, 2007a, 2007b).

By developing a standardised framework, it was hoped that a more reproducible system could be implemented, which would may one day become the industry standard. This quantitative model, based around multi-criteria decision analysis, was devised and validated by the authors. The development of this model was lengthy and time-consuming, involving several years of work. It was essential that the authors collaborated with all relevant stakeholders involved in benefit-risk assessment, to ensure that the requirements of each stakeholder were considered and integrated into their model. The authors described how newer models not based around MCDA had also been published in recent years, although it was clear that they had similar weaknesses to those described previously, since they were often based on the general models (Mussen, Salek and Walker, 2009).

#### *Qualitative models*

Qualitative models are created around the concept that experts make decisions based mostly on their experience and after a thorough review of data. They often use 'gut feeling' to make decisions, and this is obviously difficult to replicate. 'The current process of benefit-risk assessment of medicines relies primality on intuitive expert judgement' (Coplan *et al.*, 2011, p. 312). The literature shows that regulators still rely heavily on qualitative decision-making, centred on a review of data. Regulators agree that there is a great deal of work to be done with regards to standardising benefit-risk analysis. In addition to the work undertaken by the CHMP in Europe, the United States Food and Drug Administration (FDA) are also working on this issue and are in fact leading the way at the present time. In their recent publication 'Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making' (FDA, 2013) they outline their case for a complete review of their current systems and processes. Once fully qualitative, the authors stated that 'in the past, some FDA stakeholders have indicated that there is room for improvement in the clarity and transparency of FDA's benefit-risk assessment in human drug review (FDA, 2013). Consequently, the FDA accepted that work was needed to develop processes internally, and this review was completed by 2017.

### *Semi-quantitative models*

The fact that several different models exist, some adopting a quantitative approach only and others fully qualitative, divulged from the literature that that a standardised method for B-R assessment was required. In spite of this, regulators and pharmaceutical companies did not formally follow a universal procedure. Thus, by implementing a semi-quantitative approach, it would be possible to utilise the strengths of both type of assessment; established upon expert decisions concerning a quantitative analysis of the clinical trial data. Nowadays, a semi-quantitative approach emerges more often in the literature, indicating it is the preferred method by most. The need for a universal B-R framework has been well described by a number of research groups. Mussen, Salek and Walker (2009) stressed this need and several papers also discuss the concept as a whole (Coplan *et al.*, 2011; Brass, Lofstedt and Renn, 2011; Colopy *et al.*, 2015).

Coplan *et al.* (2011, p. 312) described the need to development a framework which ‘enhances transparency, reproducibility and communication of the benefit-risk balance of medicines.’ In reality, this has been a common theme throughout the literature. Without a universal framework, how are companies able to understand how regulators assess B-R? This is a difference in perspective compared to the actual model implemented, but these elements are equally important. This highlights the difficulty of implementing a universal process as there are multiple elements to consider.

Although the FDA publish documentation related to their decision-making online, they also point out that ‘while the FDA takes great care to clearly explain the reasoning behind a regulatory decision in these documents, the clinical analysis may not always be readily understood by a broad audience who may wish to understand FDA’s thinking’ (FDA, 2013, p. 1). This is because their previous methods essentially followed a qualitative approach, heavily reliant on expert judgement and it was difficult to reproduce.

The authors also describe how many stakeholders have also highlighted the need for 'regulatory decisions to be based more on a formalised and quantitative approach to benefit-risk assessment, including the assignment of weights to benefit and risk considerations' (FDA, 2013, p. 1). This is interesting as it is this type of approach that has been proposed by Mussen, Salek and Walker in their book (2009). The FDA began to develop their own framework in 2012. The initial project aimed to identify relevant stakeholders. They also piloted the new framework, including the use of MCDA, alongside their current processes in order to compare the outcomes. This project was part of a long-term strategy commenced in 2013 and completed in 2017.

#### *BRAT framework*

Around 2009 it appeared that a standardised approach was finally going to be accepted by regulatory agencies and industry. Those in the industry eventually became dissatisfied with this lack of established best practice. Several organisations collaborated to set up the 'Benefit-risk Action Team' to address the problem, and together they eventually developed the 'BRAT framework.' Through the development of a 6-step process, BRAT aimed to standardise the decision-making and communication surrounding benefit-risk assessments. The 6-stages developed were: define decision context, identify outcomes, identify data sources, customise framework, assess outcome importance, and display and interpret key BR metrics (IMI PROTECT, 2018). The development of this semi-quantitative framework was a step forward in the ultimate goal of developing a standardised approach to B-R assessment. Levitan *et al.* (2014) described how the use of this framework could be greatly enhanced by inviting patients into B-R discussions.

### *PrOACT-URL framework*

Zafiropoulos *et al.*, (2012) expanded work in this area and they eventually developed the PrOACT-URL framework. PrOACT-URL is now the EMA's generic decision-making guide with eight designated steps. The steps are: Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions. The framework covers the important aspects for structuring a decision-making problem. The framework itself is generic and can be applied to any decision-making problem, but the EMA's Benefit-Risk Project adapted PrOACT-URL is focussed on the decision-making of medicines (IMI PROTECT, 2018b).

However, even with the development of process at the regulatory agency level, recent publications (Wolka *et al.*, 2016; Smith *et al.*, 2017) suggest that some companies have still decided to take a different route with regards to the processes they implement. Wolka *et al.* (2016) described a process which was implemented within Eli Lilly, which involved submitting B-R documentation as part of marketing authorisations. Whereas Smith *et al.* (2017), from Amgen, describe their methodology for B-R across the product lifecycle.

It is a positive development that companies are publishing these methods and adding to the literature, however, it is still evidence of a lack of a universal framework which all regulators and pharmaceutical companies adhere to. This is substantiated by the fact that companies still implement their own methodologies, even with standard processes being developed by regulators. Although there has been progression and clear developments, there is still work to do.



## **Stakeholders involved in benefit-risk assessment**

The stakeholders involved in benefit-risk analysis include pharmaceutical companies, regulatory agencies as well as healthcare professionals such as prescribers (Mussen, Salek and Walker, 2009, p. 6). One key area that is addressed by Mussen, Salek and Walker (2009) is the different perspectives of professionals involved in benefit-risk analysis (2009, p. 6-8). Stakeholders have both diverse viewpoints and various priorities depending on the nature of their work. 'Since benefit-risk assessment is essentially a value judgement, it will inevitably be prone to a number of biases' (Mussen, Salek and Walker, 2009, p. 8). These biases are informed by the nature of the work of the individual making the assessment. In addition, different individuals may give different views at different times, even when presented with the same data; which demonstrates the subjective nature of the assessment process (Mussen, Salek and Walker, 2009, p. 8).

McAuslane *et al.* (2017) describe how the Centre for Innovation in Regulatory Science (CIRS) evaluated the models used for the B-R assessment of medicines. This work involved evaluating current practice and included a programme of workshops; 'bringing together members of the pharmaceutical industry, regulators, academia, patients, and other stakeholders as well as supervising doctoral research and surveying stakeholders' (McAuslane *et al.*, 2017, p. 635).

### *Pharmaceutical companies*

The primary objective of pharmaceutical companies is to demonstrate sufficient efficacy of a product to receive regulatory approval. In addition, the company would hope that healthcare professionals prescribe the medicine (Mussen, Salek and Walker, 2009, p. 7). A particular company may accept a risk depending on how likely that risk will affect the chance of the product receiving a licence. They also consider the possibility of legal liability in the event of serious adverse events (Mussen, Salek and Walker, 2009, p. 7).

### *Regulatory agencies*

Regulatory agencies take a population approach when assessing benefits and risks, in that they view the nation as a whole rather than focussing on individuals (Spilker, 1994; Cromie, 1997). They require evidence for an established and favourable safety profile. They will also consider the cost of a treatment by comparing it to treatment alternatives because the pharmacoeconomics of medicines also influences their decision-making. Regulators 'usually focus on risks more than benefits due to their responsibility for ensuring public health' (Mussen, Salek and Walker, 2009, p. 8).

### *Healthcare professionals*

Prescribers have their own unique perspective with regards to benefits. 'They assess or guess whether other doses, other medicines or a non-medicine treatment will enhance or reduce the degree or type of benefit obtained' (Spilker, 1994, p. 53). Risks and benefits may 'offset each other', for example a small risk may be cancelled out by an even greater benefit. In fact, sometimes risks 'are given greater emphasis by prescribers when compared to the risks of the disease being treated' (Mussen, Salek and Walker, 2009, p. 8). In some cases, prescribers may focus on benefits or risks depending on research data they have reviewed. This is often 'strongly influenced by the way data is presented in scientific journals and advertisements' (Skolbekkan, 1998, p. 1958).

### *Patient advocacy groups*

As the need to involve patients in B-R assessment was recognised, methods for including patients within company and regulatory processes were developed. One of the biggest challenges faced by pharmaceutical companies and regulatory agencies is accessing patients directly. There are of course the logistical challenges of meeting patients face-to-face but there are also ethical considerations too. Therefore, one successful method of linking in with patients has been for companies and regulatory agencies to collaborate with patient advocacy groups (IMI PROTECT, 2018). Often, these groups are

managed and run by patients themselves, but they may also be volunteers or healthcare professionals who work closely with the patient group of interest. Patient advocacy groups therefore act as a useful gatekeeper for pharmaceutical companies and regulatory agencies to gain direct access to patients. As such, their involvement in B-R assessment has become popular in recent years (IMI PROTECT, 2018).

### *Patients*

In general, 'regulators tend to view patients as incompetent to judge risks and benefits,' (Mussen, Salek and Walker, 2009, p. 8). However, times are changing. Patient-Public Involvement (PPI) has become increasingly important in recent years. As patients become more informed, due to increased access to information such as via the internet, their well-informed opinions are increasingly important. The National Institute of Health Research (NIHR) explain that PPI leads to higher-quality, patient-focussed research which speeds up the transfer of evidence into clinical practice (NIHR, 2013, p. 4).

Patients and the public can participate in research in a number of ways. Most often, their participation involves working with researchers, clinicians, research managers and health economists. Patients are now often involved in 'setting research priorities, identifying research questions, influencing research design, assessing protocols, being active partners in the research process itself, ensuring results are published and speaking about the value of research' (NIHR, 2013, p. 4). Although patients are now involved in many different aspects of research design and management, this PhD thesis focuses on the involvement of patients in benefit-risk assessment.

### *Different perspectives*

One key aspect of clearly defining the stakeholders involved in B-R assessment is the variety of perspectives that these stakeholders will ultimately exhibit. This is the reasoning why involving patients in B-R assessment is key, mainly because they will view benefits and risks differently to the views of pharmaceutical companies and regulatory assessors.

Arnardottir *et al.*, (2012) explored this very question and revealed that patients would be willing to accept greater risks when compared to the opinions of healthcare professionals. This was also verified later when it was highlighted that 'regulators may value major benefits and risks of drugs for an individual patient mostly in the same way as doctors and patients, but differences may exist regarding the value of minor or short-term drug effects' (Mol *et al.*, 2014, p. 979). These findings are evidence of why patient involvement is so important, as the acceptance of risk may very well determine the decision of a regulator who way well have been unsure of their decision. However, Arnardottir *et al.*, (2012) also ascertained how risk communication is so important to ensure that patients fully understand what is being presented to them.

### **Science communication and risk perception**

Science communication is now an academic discipline of its own, which developed from the idea that the approaches taken to present science to lay audiences should follow a standardised methodology. Bjornson (2004) described how a lack of understanding of risk is an issue. Also, the patients' need for an effective treatment may in fact allow them to take risks which are inappropriate. Bjornson (2004) focussed on the interpretation of risk which can be different between individuals and the wider population. More recently, it was elucidated how involving patients in their risk management is an effective tool in reducing overall risks associated with their condition (Coleman and Muir, 2015). The FDA advises patients in their guidance documentation regarding use of medicines that they must accept certain risks in order to benefit from a drug. For example, a patient may accept greater risk in a life-threatening disease 'in the hope of getting the benefits of a cure or a longer life' (Mussen, Salek and Walker, 2009, p. 8). In the case of a minor illness, a patient may only accept a limited risk of adverse events. This concept appears many times in the literature and is clearly a concern for stakeholders.

Nair *et al.* (2002, p. 105) also came to a similar conclusion. They found that 'patients and clinicians each appear to have a different understanding of what and how much information patients should receive about medications,' including information related to drug risks. This indicates that the patient and clinician have different priorities; which would ultimately affect their decision-making. However, Nair *et al.* (2002, p. 105) did highlight that 'feedback from patients can be used to develop patient-oriented treatment information,' therefore, patient involvement is a useful undertaking. What is essential, however, is the understanding of risk and the communication of that risk. Risk perception changes depending on how an idea is presented, so this is clearly an area of importance when involving patients in B-R assessment.

### **Patient and public involvement (PPI)**

McKevitt *et al.* (2015, p. 3248) stated that 'increasingly, patients are being repositioned as active partners in the production and maintenance of health, rather than as passive recipients of health care.' It was also identified that 'there is now an international body of evidence to demonstrate the benefit of patient and public engagement in health' (Corrie and Finch, 2015, p. 9). This research group emphasised that 'shared decision-making programmes encourage clinicians and patients to collaboratively select a course of action based on both clinical evidence and the patients' informed preferences' (Corrie and Finch, 2015, p. 10).

Their comments are mainly in reference to research around PPI in healthcare, though the latter statement in particular has specific relevance to the topic of patient involvement in B-R assessment. Foot *et al.* (2014) go further, by describing how caregivers and family members should also be involved, especially in situations where the patient may require additional support when making treatment decisions.

The UK's National Institute of Health Research (NIHR) implemented a detailed strategy of patient and public involvement in research in 2013. This strategy contributed greatly to real change within the UK's research environment.

Not only did researchers gain awareness and understanding of the importance of PPI, but they also began the process of including patients within their research design. This would ultimately result in studies which are more appealing to patients and increase patient recruitment and retention. This strategy included development of the INVOLVE initiative. 'INVOLVE is an initiative to support active public involvement in NHS, public health and social care research. It is one of the few government funded programmes of its kind in the world' (INVOLVE, 2018).

However, there are also challenges with implementing PPI effectively. Gibson *et al.* (2012, p. 1) 'identified some of the major inherent weaknesses of a monolithic, single-track model of patient and public involvement in the management and running of health and social care systems.' A one-size-fits-all methodology does not work in practice, as some social groups do not involve themselves as much as others, whether by choice or by situation, therefore there is a risk that PPI is not fully representative. Williamson (2013) describes how some marginalised groups are often excluded from PPI initiatives. In addition, Komporzozos *et al.* (2016) and Martin (2008) highlight how PPI initiatives can be hindered by the 'power and knowledge differentials between patients and clinical professionals' (Martin, 2008, p. 1757).

There is also another risk, highlighted by the findings from the Public Involvement Impact Assessment Framework Study Group, who stated that there is a risk that some researchers may only take a tokenistic approach to PPI. In their paper, the group state that when PPI is undervalued, it 'leads to tokenism in research practice. Tokenism fails to demonstrate value; thus, PI is perceived as not adding value to health and social care research' (PiiAF, 2013, 2014). Staniszewska (2015) may provide evidence of why a tokenism approach is sometimes taken. It may be down to a lack of experience or understanding of PPI itself.

It was identified that researchers need greater training and support with regards to how to undertake patient and public involvement initiatives adequately. In addition to the process itself, researchers also need assistance in developing the relevant competencies they need, such as 'collaboration skills, listening skills, insight, empathy and an understanding of how different values and motivations can influence patient and public involvement in research' (Staniszewska, 2015). This is a valid point and without adequate education there is a risk that PPI will not be implemented effectively.

### **The concept of the 'expert patient'**

In addition to the general principles of PPI, Corrie and Finch (2015) also present a new concept, specified as the 'expert patient,' which has been emerging in the literature in recent years. The expert patient is defined as a patient who fully understands their condition and the treatments available to them. They often participate in initiatives to assist in educating others about their condition, from patients through to clinicians and other healthcare providers. This different perspective can be useful as it enables a deeper understanding of a patient's condition, particularly with respect to how it affects them on a personal level.

Corrie and Finch (2015, p. 20) explain that 'while patients have traditionally been regarded as passive users of the NHS, patients are engaging with their health in different ways outside of NHS services.' Surveys within the NHS 'consistently show that patients want more information about their health conditions and treatment options and the skills to self-manage their condition' (Corrie and Finch, 2015, p. 10). Patients also now expect to be involved in their treatment decisions and interestingly, they are not only engaging more with clinicians, they are also engaging with each other. For example, in recent years several 'online peer-to-peer support networks to enable patients to share their experiences and learn from each other's experiences have emerged'; such as 'Patients Like Me' (Corrie and Finch, 2015, p. 26).

## **Involving patients in benefit-risk assessment**

Involving patients in the research process is not a new concept; however, involving patients in the area of benefit-risk analysis is without a doubt a recent development. It has been identified by several parties that patients have a vital role to play as they can offer a different and unique point of view. This is because patients, who are taking medications for their various conditions, may view benefits and risks very differently when compared against the views of pharmaceutical companies or regulatory assessors.

Patients tend to 'view benefits in terms of how their symptoms improve, by how much and for how long' (Mussen, Salek and Walker, 2009, p. 9). In addition, patients view risks with respect to their chance of having an adverse reaction or a lack of effect resulting in a relapse of their underlying disease (Mussen, Salek and Walker, 2009, p. 9). It is important to note that patients may sometimes 'focus excessively on any risks to which their attention is drawn' so the 'perception of risk may therefore be different from actual risk' (Mussen, Salek and Walker, 2009, p. 9).

In essence, patients' opinions are 'often very personal, subjective value judgements that can only be based on religious, philosophical, and social values' (Veatch, 1993). It is therefore essential that an individual is given all the information and not only material on the benefits or side-effects, so that they can make an unbiased decision. Many factors influence how a patient views the benefit and risks of a particular treatment. They are 'influenced by the media, by healthcare professionals and by friends and family' (Mussen, Salek and Walker, 2009, p. 10). This makes for a very complex picture, which can be unique to every individual. In addition, the way in which a patient makes their assessment is strongly influenced by the way in which the data is presented.



For example, if side effects have been emphasised by a healthcare professional, when in fact the risk is low, the patient may still be influenced negatively. However, even with these challenges, one key statement made by Mussen, Salek and Walker (2009, p. 10) is of particular importance and interest:

‘Research has demonstrated that, despite the fact that lay people sometimes lack certain information about hazards, their basic conceptualisation of risk is much ‘richer’ than that of the experts and reflects legitimate concerns that are typically omitted from expert risk assessments.’

In their book entitled ‘Benefit-Risk Assessment in Pharmaceutical Research and Development,’ Sashegyi, Felli and Noel (2014, p. 39) have described the importance of the patient’s perspective. These authors drew attention to how ‘the FDA and industry have inherent biases regarding drug approval processes. Hence, the FDA worries foremost about risk while industry focuses on benefit profiles.’ The authors discuss how having two ends of a spectrum is not an adequate tactic to the problem. Patients can be the ‘voice of reason in decision-making processes, tempering industry and regulatory predispositions to ensure progress’ (Sashegyi, Felli and Noel, 2014, p. 39). This is a valid approach as there are multiple places in between. They state that ‘no party is better able to assess a drug’s acceptable risk than those living with the illness the drug is designed to address’ (Sashegyi, Felli and Noel, 2014, p. 39). Although this is a valid opinion, it is not fair to state that only the FDA and industry have their intrinsic biases. It is inevitable that patients have their inherent biases too. The fact that several international stakeholders are now implementing projects to include the patient’s perspective in drug development and benefit-risk demonstrates it is highly topical and requires further research. These initiatives are described subsequently.

## **Current initiatives to involve patients in benefit-risk assessment**

### *FDA*

The FDA was one of the first regulatory agencies to include the patient's perspective in their programme for developing the benefit-risk assessment process. They initiated a project entitled 'Patient-Focused Drug Development' in 2012, which has since been incorporated into their long-term strategy.

The FDA makes it clear that patients have a unique perspective with regards to a drug's benefit and risk profile and they understand how patients can offer valuable contributions to the drug development and subsequent review process. However, they recognise the need for a systematic approach of obtaining patient views and opinions (FDA, 2013a). The authors describe how several programmes exist to facilitate patient representation in other ways, sometimes accessing patient advocacy groups, but the focus has not previously been on benefit-risk assessment.

The programme, which has been published on the FDA's web site, described how a series of workshops were undertaken with patients suffering from various diseases so they could be questioned on their condition and current drug therapy. The ultimate aim was to not only to gain the patient's perspective on the condition and their current therapy, but to also help identify an unmet medical need, which could help with drug development programmes (Mullen, 2012).

This approach was very much qualitative in nature. The workshops were facilitated by experts in B-R assessment in combination with patient representatives. The methods utilised open forums where patients, and in some cases, family members and carers, could all contribute to the discussion. The meetings were recorded and transcribed, and the transcripts are available for public review. Thematic Analysis was undertaken and the themes of most importance to patients were documented. Mullard (2013) reviews the first meetings of the FDA's 'Patient-focused drug development' programme.

The FDA aimed to facilitate up to twenty meetings with patients and patient advocacy groups over the five-year programme. They selected a range of patient groups for inclusion within the programme, which are displayed in Table 2.1 (as listed in Box 1, page 652, Mullard, 2013). The range of conditions which were included is interesting as many focussed on rare diseases, which, the FDA, had concluded is where the patient’s perspective can be most valuable.

It should also be noted that in some cases parents were invited to speak on behalf of their children who had a rare condition. For example, during the ‘Neurological manifestations of inborn errors of metabolism’ workshop, parents of children with Batten’s Disease offered their contributions (FDA, 2014a).

**Table 2.1: Patient-Focused Drug Development – Conditions included in the FDA’s programme (in order of meeting date, FDA, 2013b)**

<b>Year and patient group / condition</b>
2013: Narcolepsy; HIV, Lung Cancer, Chronic Fatigue Syndrome
2014: Sickle Cell Disease, Fibromyalgia, Pulmonary Arterial Hypertension, Neurological Manifestations of Inborn Errors of Metabolism, Haemophilia A and B, Idiopathic Pulmonary Fibrosis
2015: Female Sexual Dysfunction, Breast Cancer, Chagas Disease, Functional GI Disorders, Parkinson’s and Huntington’s Disease, Alpha-1 Antitrypsin Deficiency
2016: Non-tuberculous mycobacterial infections, Psoriasis, Neuropathic pain associated with peripheral neuropathy, patients who have received organ transplant, Sarcopenia, Autism, Alopecia, Hereditary Angioedema

The first three meetings involved patients with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS), lung cancer and HIV and the opportunities plus challenges associated with systematically integrating the patient perspective into drug reviews were emphasised (Mullard, 2013, FDA, 2013b).

One of the aims of these meetings was to inform the FDA's benefit-risk framework. 'While developing the framework, the FDA recognized [*sic*] that two key factors – analysis of the condition and current treatment options – required more patient input' (Mullard, 2013, p. 652). It was clear that there were currently limited opportunities for patients to voice their opinions with regards to drug development. The FDA therefore hoped to 'fill this gap' and ultimately improve other policies throughout the agency as a result (Mullard, 2013, p. 652). Mullard also describes how the National Health Council (NHC) 'participated in early discussions around the need for both the benefit-risk framework and the patient-focused drug development programme' (Mullard, 2013, p. 652; FDA, 2013b).

The NHC could also appreciate the benefit of incorporating patient views in this context. The meetings were conducted in a manner which 'allowed both patients and patient advocates to discuss their disease symptoms, treatment options and the side effects they endure' (Mullard, 2013, p. 652). One interesting point to note was how the meetings developed differently depending on the indication under discussion. For example, the ME and CFS meeting involved detailed discussion on how pain and fatigue affect the patient's lives on a daily basis, as these are possibly the major issues that this patient group endures. The HIV group, however, focused on their difficulties around drug side effects and drug-drug interactions (Mullard, 2013, p. 652; FDA, 2013b).

This is interesting as it demonstrates how different patient groups may focus on very different issues when it comes to their condition and treatment, depending on how it affects their daily lives. Mullard recognised 'the challenge

of capturing a sufficiently diverse set of patient perspectives from brief meetings, especially when sub-populations have different needs and views' (Mullard, 2013, p. 652). For example, the lung cancer meeting was only comprised of patients who were well enough to travel. This could have signified that their disease and therefore experiences were not the same as those patients unable to travel due to the severity of their illness.

The views described may therefore not have been truly reflective of the entire patient group. This is a challenge and something that must be addressed. The HIV patient group also flagged up additional challenges since the meeting did not include many patients who were recently diagnosed with the disease. It was of note that during this meeting, the discussion turned towards participation in clinical trials. 'It is now evident that recruitment into HIV clinical trials is becoming increasingly difficult, due to the advances and success that drug developers have achieved with antiretroviral therapy' (Mullard, 2013, p. 652). Thus, it was concluded that 'the patients most likely to enrol and experiment with new regimens could not discuss their concerns' (Mullard, 2013, p. 652) as they were not present at the meeting. Mullen later described how it was clear from the early meetings of the programme 'just how important it is to ensure a broad a group of patients are represented at the meetings as possible' (Mullard, 2013, p. 652).

To assist with this matter, the NHC has developed a 'Patient Stratification Tool' to 'help identify patient sub-populations, differences in disease impact and variations among the population in terms of treatment and management options' (Mullard, 2013, p. 652). The goal of the tool was to 'provide a way for patient groups to systematically organize [*sic*] issues, stratify their patient population, and identify key topics of focus in preparation for meetings' (NHC, 2013). This tool could also be used to 'ensure that patient input was stratified and applied appropriately during benefit-risk decision-making' (Mullard, 2013, p. 652; FDA, 2013b). Another key requirement of the project that the FDA was keen to implement was to allow patients unable to attend meetings in person the opportunity to give their opinions. This was essential to ensure

that a range of views were obtained. It may be that some patients were too unwell to attend the meeting in person, however, their views may well have been some of the most important to obtain; especially if the reason they were unable to attend the meeting was due to the severity of their disease or perhaps even due to drug side effects. The FDA therefore ‘explored alternative ways of engaging remote participants in real-time’ (Mullard, 2013, p. 652). For example, the use of online questionnaires (Mullard, 2013, p. 652).

#### *European Medicines Agency*

Like the FDA, the EMA’s approach to patient involvement in B-R assessment has also been qualitative in nature. Individual Member States, such as France, began work on their own projects (Affsaps, 2006), before collaborating at the European level. ‘In addition to the Benefit-Risk Methodology Project, the EMA supported the evaluation of methodologies for the inclusion of the patient voice in the decision-making process’ and created a road map to do this, commencing in 2014 (Muhlbacher *et al.* 2016, p. 735).

The EMA’s remit is to ‘help ensure that over 500 million European citizens, from very varied environments and cultures, are provided with safe and effective medicines.’ The EMA, therefore, ‘has been at the forefront of efforts to involve patients as critical stakeholders in the regulatory process and works extensively with patient and consumer representatives’ (EMA, 2018).

At the EMA, benefit-risk evaluation is performed primarily by the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC). The EMA note in their reports (EMA, 2014a, 2014b, 2014c, 2014d) that ‘patient representatives are also involved in the work of other EMA scientific committees and working parties’ (EMA, 2014a, 2014b). As such, the EMA argued that ‘patients should be consulted in all cases where their involvement can bring added value to the benefit/risk discussion’ (EMA, 2014c, p. 1).

In this context, the EMA states that ‘patients’ representatives already participate within the EMA scientific committees as: members, who act in the same way as all other members or ‘experts’, who advise the committee on specific issues and are selected for their relevant expertise, experience or knowledge; they bring a real-life experience of the disease and its current therapeutic environment.’

Therefore, the EMA are one of the first examples of a regulatory agency employing an ‘expert patient’ within their committee meetings. These expert patients ‘usually only attend part of a meeting to answer specific questions raised by the committee and do not take part in committee conclusions or decisions’ (EMA, 2014a, p. 1).

They must maintain confidentiality, declare any conflict of interest and abide by the EMA code of conduct’ (EMA, 2014a, p. 2). In addition, the EMA also ‘invites representatives of an organisation(s), who express the views of a patient organisation(s) related to a specific issue when requested by a committee,’ therefore, the use of patient advocacy groups by the EMA is well documented (EMA, 2014a, p. 2). It is now a long-term objective of the EMA to interact with patients in more effective ways (CRF Advisor, 2015).

Bernabe *et al.* (2014) completed a study examining patient representatives’ contributions to the B-R assessment tasks at the EMA. This was a well-executed study; however, some interesting elements of the publication stand out. The first is the population sampled: fifteen participants were regulatory staff and only five were patient representatives. In addition, it was interesting how knowledgeable the patient representatives were; quoting pharmacovigilance terminology and other terms associated with B-R assessment. It is fair to say that the majority of patients would not have the understanding or background to comment on B-R assessment at this level. Therefore, are these patient representatives’ truly representative of patients? It is argued that they are not.

**Table 2.2 – Summary of the contributions of patient representatives in the benefit-risk assessment task of scientific communities (adapted from Bernabe *et al.* 2014).**

Benefit-risk tasks	Contributions of patient representatives
Benefit-risk analysis	Additional inputs in the benefit-risk picture, such as experiential information regarding the pathology or some other aspects that regulators might find negligible but may in fact be important from a patient's perspective.
Benefit-risk evaluation	Providing a concrete basis for the values and weights given to specific benefits and risks by concretizing and making explicit the significance of these benefits and risks (by providing real-life impact of certain interventions on patients, for example).
Decision-making	Especially within areas where the patient perspective is necessary or pressing, validating that the risks of an indication are indeed acceptable for the patients considering the benefits (i.e., provide extra confidence on the decision).

*Lilly's MEET Initiative*

It is not only regulators that have initiated projects related to patient involvement. The pharmaceutical company Lilly commenced a series of workshops entitled 'Medicine Evaluation Educational Training' or 'MEET' workshops. This programme aimed to involve patients at all stages of medicines development including drug evaluation and assessment. The programme was divided into several modules including how health technology assessment (HTA) is undertaken in the UK as well as how patient advocacy groups can be involved not only in HTA but also in regulatory decision-making regarding drug evaluation.



### *IMI PROTECT*

As the FDA's project gained more exposure, and as companies such as Lilly communicated their findings, more and more collaborations began to develop over the period of 2013-present. Wolka *et al.* (2017) stressed that the most effective partnering in B-R discussions are those which involve patient advocacy groups, pharmaceutical companies and regulatory agencies; all working together. The IMI PROTECT consortium is a 'collaborative European project that comprises a programme to address limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance.' This large initiative is coordinated by the EMA and GSK (IMI PROTECT, 2018a). The EMA observed the FDA's project carefully, and after undertaking their own patient involvement projects, they identified that the best way forward was through a collaboration with the pharmaceutical industry and academia. Focusing very much on B-R methodology, IMI PROTECT highlighted the need to involve other organisations in the process; namely patient advocacy groups as well as patients themselves.

### *PREFER*

PREFER is one of the most recent projects that has been established. The project is in its early stages of development however it aims to 'establish recommendations to support development of guidelines for industry, regulatory authorities and HTA bodies on how and when to include patient perspectives on benefits and risks of medicinal products' (PREFER, 2018). This is an area of the literature that is covered in great depth: the development of patient preference studies.

A patient preference study is a quantitative study where patients are able to make choices based on their preference. Quantitative benefit-risk preference-elicitation methods include discrete choice experiments, rating scales, threshold technique, standard gamble and conjoint-analysis (Hauber *et al.*, 2013; Hiligsmann *et al.*, 2014).

Bowling and Ebrahim (2001) and Acquadro *et al.* (2003) explored different ways in which patient preferences could be incorporated into a B-R assessment framework. Their research focussed on patient reported outcome measures (PROMs), an effective way of obtaining information directly from patients (Nelson *et al.*, 2015). Further work was undertaken by Egbrink and IJerman (2014) and van Til and IJerman (2014) who drew attention to the value of quantitative patient preferences directly in regulatory decision-making. Johnson and Hauber (2008) and Danner *et al.* (2011) also presented their methods of undertaking quantitative patient preference studies. The study completed by Danner *et al.* (2011), however, looked at their use with regards to Health Technology Assessment. In addition, Wolka *et al.* (2017) presented an example where patient advocacy groups representing psoriasis patients were able to contribute effectively, when undertaking a preference elicitation study.

Improved patient involvement has the potential to drive medicines development, as more relevant and impactful patient outcomes will increase efficiency, whilst make the drug lifecycle more productive (Hoos *et al.*, 2015, p. 929). It will also contribute to a better prioritisation of candidate molecules, 'and by addressing barriers to patient participation, enhanced recruitment and retention in clinical trials' (Hoos *et al.*, 2015, p. 929). If a universal framework for patient involvement is ever to be adopted, a unique partnership will be required between all relevant stakeholders; who will need to implement a change of culture within their organisations (Smith *et al.*, 2016)

Using the knowledge gained from the existing literature, the research study employed during this programme of PhD research was developed. Chapter III describes the research strategy which was employed for this research study and the justification for the approach taken.

# **Chapter III: Research strategy and methodological framework**

## **Introduction**

Chapter III commences with the overall research strategy which was employed for this study. The chapter describes how the research methods were selected, the justification for these decisions, and a critical analysis of each research method which was utilised. Chapter III focusses on the justification for selection and the theory behind these research methods, however, the practical details of exactly how they were implemented within this study are included at the start of each individual results chapter (Chapters IV, V and VI).

## **Research strategy**

Biggam (2015) explained how a clear research strategy is essential for undertaking a successful research study. A research strategy is defined as ‘a description of how the research study is implemented; the strategy taken to complete the empirical study’ (Biggam, 2015, p. 150). The research strategy for this research study involved a semi-quantitative approach, described by Creswell (2014) as ‘mixed-methods;’ utilising both quantitative and qualitative methods. The decision to describe this study as ‘semi-quantitative’ rather than ‘mixed methods’ was attributed to the fact that this is the standard terminology used within industry (in the context of the B-R assessment of medicines).

## **Strategy for the review of literature**

The research strategy must be clearly defined and it must be justified. Once the strategy has been decided, it is essential that a thorough investigation is completed into the current literature around the topic of the research study.

Creswell (2014) asserted that a review of literature must be completed throughout the period of research and must be focussed around the topic under investigation. It is important to undertake the literature review on commencement of a period of research, however, this is not an individual exercise. The literature review, is by necessity, an ongoing process. This is to ensure that new literature was identified and any recent research findings which may be relevant to the study were incorporated. Thus, a literature review was commenced in March 2013 and an annual review of the literature was undertaken throughout the period of the research study (2013-2018). Initially, the literature review focussed on the benefit-risk assessment of medicines. The following key words were searched: benefit-risk, benefit-risk assessment, benefit-risk assessment of medicines. The literature identified from these search terms was very much focussed on the quantitative methodology around benefit-risk assessment. Therefore, the next stage involved modifying the search criteria to include 'qualitative' and 'mixed-methods.' Although this did identify some literature relevant to the research study, it was still not sufficiently focussed.

Mussen, Salek and Walker (2009, p. 8) describe the key stakeholders involved in benefit-risk assessment of medicines. The search terms were therefore modified again to include the following terms: 'stakeholders involved in benefit-risk assessment,' and 'stakeholders benefit-risk'. This search produced relevant literature which included those studies described in Chapter II (Review of Literature) involving pharmaceutical companies and regulatory agencies, as well as patient advocacy groups.

Finally, the literature review search criteria focussed on patient involvement by using the following terms: patient public involvement, patient participation, patient's perspective and patient preferences. In addition to the topic of patient participation in the benefit-risk assessment of medicines, literature about the following related topics were also reviewed: science communication, risk communication and risk perception and patient and public involvement in clinical research.

## **Methodological framework**

When developing the research proposal, it was important to identify the different approaches that could be adopted in the research. In this connection, Creswell (2014) delineated the three different approaches to research: (a) qualitative, (b) quantitative, and (c) mixed methods, or semi-quantitative as portrayed in this thesis. 'The three approaches are not as discrete as they first appear' (Creswell, 2014). This statement is interesting as it did not become clear until late into the research process. When designing the research proposal, with limited experience in qualitative research in particular, the study design appeared to be clear. However, it was only after starting the research and experiencing the differences in the available approaches that this was understood. There were multiple examples of where both quantitative and qualitative elements were relevant within this programme of PhD research, and sometimes these methods were not clearly segregated.

Qualitative research is described as 'an approach for exploring and understanding the meaning individuals or groups ascribe to a social or human problem. The process of research involves emerging questions and procedures, data typically collected in the participant's setting, data analysis inductively building from particulars to general themes, and the researcher making interpretations of the meaning of the data' (Creswell, 2014, p. 4). Quantitative research is described as 'an approach for testing objective theories by examining the relationship among variables. These variables can be measured, typically on instruments, so that numbered data can be analysed using statistical procedures' (Creswell, 2014, p. 4). Semi-quantitative methodology refers to a combination of these approaches. This term, used regularly by regulatory agencies and pharmaceutical companies, refers to a 'mixed-methods' approach. 'This approach to inquiry involves collecting both quantitative and qualitative data, integrating the two forms of data, and using distinct designs that may involve philosophical assumptions and theoretical frameworks' (Creswell, 2014, p. 4).

With a focus on qualitative methods, it was also important to recognise how theory relates to practice. Gray (2013) described how the choice of method used to gather data is not only influenced by the research methodology employed, but also the theoretical stance of the researcher. Braun and Clarke (2013, p. 27) underline how, 'in setting out a framework for research practice, methodology relies on ontology and epistemology'. Firstly, qualitative research is 'underpinned by ontological assumptions.' Ontological positions describe the 'relationship between the world and our human interpretations and practices' (Braun and Clarke, 2013, p. 27). There are many variations which can be placed along 'the ontology continuum', ranging from 'relativism' on one side, 'realism' on the other and 'critical realism' placed centrally (Braun and Clarke, 2013, p. 27). With that in mind, the research strategy employed for this programme of PhD research, from the perspective of developing a framework for involving patients in B-R, was from a critical realist position. 'Realism assumes a 'knowable world,' which is comprehensible through research' (Braun and Clarke, 2013, p. 27).

Furthermore, Braun and Clarke (2013, p. 27) also explained how qualitative research is also 'underpinned by epistemological assumptions.' The fundamentals of epistemology are based around the 'nature of knowledge' and primarily refer to 'what counts as legitimate knowledge' (Braun and Clarke, 2013, p. 27). There are a number of epistemological stances, including positivism, post-positivism, constructionism, and contextualism. 'Positivism assumes a straightforward relationship between the world and our perception of it' and 'requires demonstration of reality through objective (unbiased) collection of data.' Post-positivism, however, views the search for the 'truth' as achievable, but 'acknowledges that researchers are influenced by their contexts' and therefore influence their research (Braun and Clarke, 2013, p. 27). Interpretivist research 'is guided by the researcher's set of beliefs and feelings about the world and how it should have been understood and studied' (Denzin and Lincoln, 2005; Levers, 2013).

Yet, the very nature of qualitative research means that ontological and epistemological positions can inevitably change, depending on the situation and the findings which are identified from within the data. This, with regards to this programme of PhD research, the philosophical position of the researcher was that of constructionist. The constructionist paradigm 'is conceptualised by having aspects of both the postpositivist and interpretivist paradigms – ontological critical realism with epistemological subjectivism.' Levers (2013) described how in a constructionist paradigm, 'meaning is created through an interaction of the interpreter and the interpreted' therefore, 'knowledge of the observed is constructed rather than discovered' (Levers, 2013).

It was clear that patient involvement in B-R assessment was a new area of investigation. The FDA and EMA were taking a qualitative approach to patient involvement, although, with an ever-increasing volume of literature on quantitative patient elicitation and patient preference studies, a combination of these approaches would be an appropriate strategy to employ. With this in mind, when considering a framework for involving patients in B-R assessment, it was proposed that a mixed-methods or 'semi-quantitative' approach could potentially be most effective. The focus of this thesis, however, was to test and validate one element of the proposed framework: using qualitative focus groups to obtain rich data on the patients' experience, their disease and their treatment.

## **Data collection techniques and analysis**

### *Phase I: Surveys*

Braun and Clarke (2013, p. 134) describe how 'qualitative surveys, at their most basic, consist of a series of open-ended questions about a topic, and participants type or hand-write their responses.' This form of qualitative research is self-administered, meaning that it is important that participants are given enough information in advance of the survey for them to understand how to complete it.



There are three main types of survey: hard copy, email and online (Braun and Clarke, 2013). Due to the population that would be surveyed, the strategy undertaken for phase I was by using online surveys. 'Online surveys require the use of specialist software, such as *SurveyMonkey*' (Braun and Clarke, 2013), therefore, this software was used for phase I of the research. This was the most convenient option, as it was known in advance that it was likely that participants would span multiple organisations across a range of countries. Details of the exact methodology used for phase I of the research will be described in Chapter IV.

#### *Phase II: Semi-structured interviews*

During phase I of the research, participants were invited to participate in phase II, involving semi-structured interviews. With this approach, an interview guide is prepared in advance of the interview, hence the name 'semi-structured,' however, this guide is not strictly adhered to, enabling the interview to take a natural course (Braun and Clarke, 2013). This approach enabled richer data to be collected; giving the participants the opportunity to build upon themes in their own words. Details of the exact methodology used for phase II of the research will be described in Chapter V.

#### *Phase III: Focus Groups*

Braun and Clarke (2013) describe how 'using a group discussion format has become increasingly popular way to collect data from participants.' The difference between semi-structured interviews and focus groups is that the latter collects data from 'multiple participants at the same time' (Braun and Clarke, 2013). They often involve a 'relatively unstructured, but guided, discussion focussed around a topic of interest' (Braun and Clarke, 2013). The researcher leading the discussion is called a 'moderator', rather than an 'interviewer' (Braun and Clarke, 2013). This is because the moderator is not asking direct questions as with an interview, although some questions of course are involved, but rather they lead a discussion; which is hopefully generated between participants (Braun and Clarke, 2013).

It was decided that this would be the most appropriate method of collecting data from patients directly. Details of the exact methodology used for phase III will be described in Chapter VI.

#### *Sample size and saturation*

Qualitative research tends to use much smaller sample sizes when compared to quantitative research (Braun and Clarke, 2013). Nevertheless, although the sample size is of less importance, for example, research has been previously undertaken with only a single participant, the concept of 'saturation' is paramount. Saturation, an important aspect of GT, 'typically refers to the point when additional data fails to generate new information' Braun and Clarke, 2013). This concept was, therefore, applied to all phases of this programme of PhD research.

#### *Coding and the generation of themes using TA and GT*

Another reason why *SurveyMonkey* was selected as the software of choice for the online surveys was the ease at which qualitative textual data can be coded and analysed (Braun and Clarke, 2013). The textual data was coded and analysed using 'thematic analysis' and the themes generated were used to influence decision-making in the later phases of the research study. To meet the ultimate aim of developing a semi-quantitative framework for involving patients in B-R assessment, it was decided a Grounded Theory approach would be most suitable. TA allows for the generation of themes within a topic, however GT goes further. By using the data to generate theories. GT focuses on 'social and social psychological processes within particular social settings' (Charmaz, 2006), and allows the researcher to 'construct theories' based on the data generated, rather than by searching for theories within the data' (Charmaz, 2006). GT can be viewed as a methodological approach utilising a series of methods, one of which is TA. There is a risk, however, that GT is frequently misunderstood.

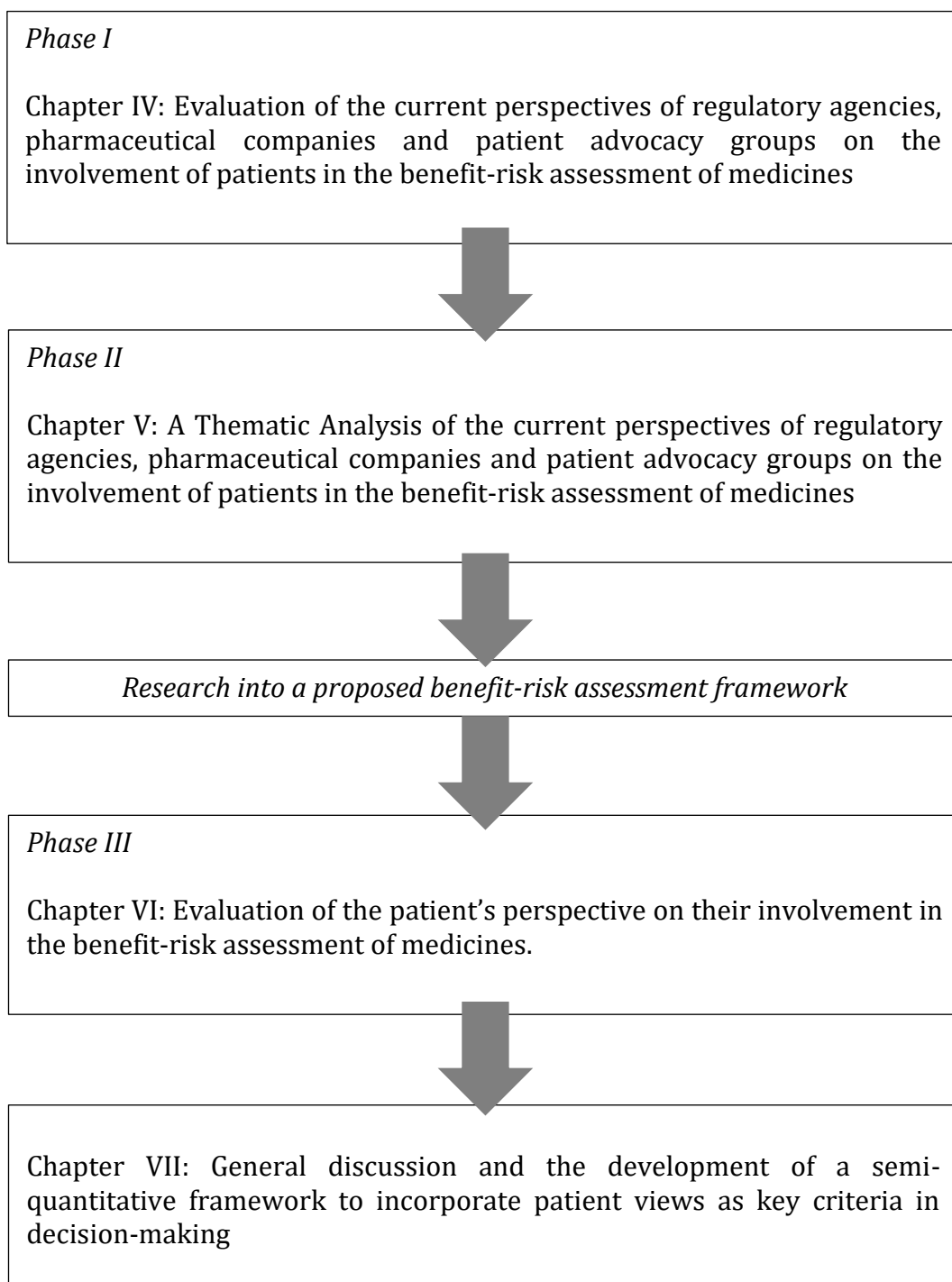
Timonen, Foley and Conlon (2018) describe the essential elements in undertaking GT: '(1) taking the word 'grounded' seriously, (2) capturing and explaining context-related social processes, (3) pursuing theory through engagement with data and (4) pursuing theory through theoretical sampling.' This research group noted the importance of remaining objective while recognising reflexivity: how the researcher influences the creation of data by being an active participant in its creation.

Finally, Bringer (2004) described how 'most authors agree that transparency is essential when communicating the findings of qualitative research.' Using a standardised approach is essential, therefore, the use of software such as QSR\*NVIVO is recommended. Therefore, this software was used for the qualitative data analysis throughout all phases of the research study.

### **Study plan and data collection**

The research strategy involved three phases. In phase I, a survey was submitted to (1) pharmaceutical companies and regulatory agencies and (2) patient advocacy groups and charities across Europe, to obtain their opinions on involving patients in B-R assessment. The qualitative survey data was analysed using Thematic Analysis (TA). Based on the findings, phase II was implemented, where individuals from regulatory agencies, pharmaceutical companies and patient advocacy groups participated in semi-structured interviews, to identify themes around patient involvement and to establish rich data around the current challenges. This data was used to inform the development of a novel framework, which was tested in phase III; where qualitative focus groups were conducted with patients. The semi-structured interview and focus group data were investigated using a Grounded Theory (GT) approach. The research strategy involved three phases, shown in Figure 3.1 – Study flowchart on Page 47.

**Figure 3.1: The study flowchart**



## **Research training**

It was important to undertake training to be fully equipped to undertake this research study. The first course undertaken was that of 'qualitative research methods,' which focused on how to undertake semi-structured interviews and focus groups, the process for undertaking thematic analysis and how to report qualitative research. The second course was about the use of the 'QRS\*NVIVO software program.' This training described the software, how to initiate a project and how to use the software to code and subsequently analyse a qualitative dataset. And finally, training was received in how to work with patients who were undergoing difficult times; important when interviewing patients about their conditions, some of which are serious in nature. Evidence of research training is filed in Appendix I.

## **Peer review**

As part of the research ethics application, evidence of peer review was required. After attending research training in qualitative research, the researcher identified a qualitative researcher who would be appropriate to act as an independent peer reviewer of the study design and study set-up. The letter of peer review is filed in Appendix II.

### **Researcher's perspective and reflexivity**

An important consideration for the design and completion of this programme of PhD research was the researcher's own background and perspective related to the subject under investigation. Braun and Clarke (2013, p. 307) describe the importance of 'owning your perspective' as a researcher – known as 'reflexivity' – in that it is essential to reflect on how a researcher's values and interests can influence the process of collecting and analysing data within a research study (Braun and Clarke, 2013, p. 307).

With that in mind, it was important to note that the researcher completing this programme of PhD research has over fifteen years' experience of designing, setting up, project managing and auditing clinical trials. He is well versed in research ethics and has been involved in reviewing over one hundred ethics applications for a range of study types; from early phase clinical trials in oncology and rare diseases requiring treatment with gene and cell therapy – through to later phase studies in a range of clinical indications. However, the researcher's experience regarding clinical trials is not only related to his professional life. His interest in the topic of patient and public involvement stems from personal experience of having a chronic condition: psoriatic arthritis. After receiving treatment with methotrexate, the researcher discontinued due to unacceptable adverse events. The opportunity to participate in a clinical trial of a new biologic called secukinumab then arose, which had an incredibly positive impact on the researcher's clinical outcomes. Therefore, the researcher has a positive approach to both undertaking and participating in research, based on their own experiences.

In addition, as a white, middle-class gay man, it is important to note how their own personal experiences and background may have affected the way in which they approached the study conduct - including their analysis of participants' perspectives. As a member of the LGBT+ community, the topic of diversity is important to the researcher; therefore, diversity played an integral aspect in the way in which the researcher approached to the study.

The combination of professional and personal experiences have therefore influenced the general approach to this programme of PhD research. In summary, the researcher's original perspective was that a diverse group of patients must immediately be recruited to participate in the benefit-risk assessment of medicines; however, this perspective changed during the conduct of the research – which will be further described in Chapter VII (General discussion).

**Chapter IV: Evaluation of the  
current perspectives of  
regulatory agencies,  
pharmaceutical companies and  
patient advocacy groups on the  
involvement of patients in the  
benefit-risk assessment of  
medicines**



## **Introduction**

Chapter II described the current initiatives which involved patients in B-R assessment. Several stakeholders had implemented strategies to engage patients directly in their benefit-risk assessment activities including the Food and Drug Administration in the US and the European Medicines Agency (FDA, 2013; EMA, 2014). Nonetheless, it could not be assured that the initial review of literature captured everything, as some organisations may not have felt the need to publicise their patient involvement projects. In addition, some organisations, especially pharmaceutical companies, may not have considered it appropriate to communicate information about their ongoing projects, perhaps because they were in an early stage of completion. It was therefore important to gain information on the level of involvement of patients from as many pharmaceutical companies and regulatory agencies as possible. Therefore, Chapter IV describes phase I of the research, where regulatory agencies and pharmaceutical companies were surveyed with regard to the current involvement of patients in B-R assessment within their organisations.

As limited research had already been completed within this area, for example the project undertaken by Bernabe *et al.* (2014), in the research plan it was decided to expand the types of organisations involved, not only focusing on European organisations but also involving several international stakeholders. Bernabe *et al.* (2014) reported how patient advocacy groups and patient representatives were involved at the EMA. However, there was no distinction between patient advocacy groups, charities or any examples of direct contact with patients. Nonetheless this was clear from the FDA's 'Patient Focused Drug Development', as patients, caregivers and family members were invited to participate directly. An important point which has been noted from these previous projects, however, is how differently the organisations approached their patient selection. Some, like the FDA, clearly defined 'patients', and used a stratification tool to differentiate patients with different severities of disease.

Conversely, the EMA projects did not appear to take these aspects into consideration and adopted the approach that a 'patient representative' and a 'patient' were interchangeable terms and these individuals had no tangible differences. However, this thesis argues that this is not the case. The objectives of phase I of the research study were to (1) survey pharmaceutical companies and regulatory agencies to discover the degree that patients were already included in benefit-risk assessment within their organisation and (2) survey patient advocacy groups to discover their current knowledge on the topic of regulatory benefit-risk assessment of medicines. In order to achieve these objectives, the following sub-objectives were identified.

### **Sub-objectives**

- Identify the current involvement of patients in B-R assessment of regulatory agencies and pharmaceutical companies.
- Ascertain the challenges of involving patients in B-R assessment.
- Pinpoint possible solutions to the challenges of involving patients in B-R assessment.
- Perceive the current knowledge of patient advocacy groups on the subject of B-R assessment of medicines.

## **Methods**

### *Sponsorship and study set-up*

To commence the research application process, sponsorship was requested from Cardiff University. One of the requirements of sponsorship was that a scientific review of the protocol was completed. Cardiff University Research Ethics Committee was therefore contacted and a member of the panel completed a scientific review of the protocol. Once sponsorship was agreed, the study setup could commence. Once the draft study protocol was developed, the study essential documentation was created in line with the Research Governance Framework for Health and Social Care. This included the participant invitation letter, a participant information sheet and consent form plus a demographic questionnaire.

### *Development of the surveys*

To satisfy the requirements of objectives 1 and 2 of this study, two surveys were developed, the first was prepared for pharmaceutical companies and regulatory agencies, the second being intended for patient advocacy groups. Surveying pharmaceutical companies, regulatory and patient advocate groups in a single survey was not appropriate due to the different levels of awareness of the concepts involved. Consequently, two separate surveys were developed. The survey aimed at pharmaceutical companies and regulatory agencies (Survey P-R) included questions regarding the involvement of patient advocacy groups and patients in different stages of B-R assessment, from the initial discussions through to B-R decision-making. The language was developed so that it would be easy to understand by participants. The survey for patient advocacy groups (Survey PAG), however, required additional information within it which described B-R assessment, as there was potential that participants would not have encountered the concept of B-R assessment previously. An example 'Survey P-R' can be found on page 53 and an example 'Survey PAG' can be found on page 63.

Benefit-risk assessment incorporating patient views

QUESTIONNAIRE for REPRESENTATIVES FROM THE PHARMACEUTICAL INDUSTRY OR REGULATORY AGENCIES **(Survey P-R)**

*Thank you for completing this questionnaire. The questionnaire should take approximately 15-20 minutes to complete.*

1) Which type of organisation do you work for? *Please circle*

Pharmaceutical Company	Regulatory Agency
------------------------	-------------------

Name of organisation <i>(optional)</i>	
Job Title <i>(optional)</i>	

2) Which of the following options best describes the system used by your organisation for assessing the benefit-risk (BR) of a new medicine and who is involved?

		Who is involved?		
		Please tick all that apply / comment		
		Internal Experts	Patient Representatives and/or Patient Advocate Groups	Patients
What type of system do you use?	Qualitative System			
	Semi-quantitative system			
	Quantitative System			
	Other <i>Please state</i>			

3) Patient Representatives and Patient Advocate Groups

Please read the following statements and give us your own personal opinion by circling the appropriate response below.

There is a need to incorporate the views of patient representatives and or/patient advocate groups into benefit-risk analysis (i.e. they can answer questions, provide general information on conditions and treatments, state their opinions, but not to do anything more than this)

Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
-------------------	----------	---------	-------	----------------

*Please provide reasons for your response*

--

There is a need to incorporate the views of patient representatives and/or patient advocate groups into benefit-risk evaluation and decision-making (i.e. they should receive voting rights in the overall decision)

Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
-------------------	----------	---------	-------	----------------

*Please provide reasons for your response*

--

4) Patients

Please read the following statements and give us your own personal opinion by circling the appropriate response below

There is a need to incorporate the views of patients into benefit-risk analysis (i.e. they can answer questions, provide information on how their condition and treatment affects them, state their opinions, but not to do anything more than this)

Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
-------------------	----------	---------	-------	----------------

*Please provide reasons for your response*

--

There is a need to need to incorporate the views of patients into benefit-risk evaluation and decision-making (i.e. they should receive voting rights in the overall decision)

Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
-------------------	----------	---------	-------	----------------

*Please provide reasons for your response*

--

5) What is your personal opinion on the perceived benefits/positives of incorporating patient views in benefit-risk assessment? *Please provide reasons for your answer*

6) What is your personal opinion on the perceived risks/negatives of incorporating patient views in benefit-risk assessment? *Please provide reasons for your answer*



7) What do you perceive are the barriers to involving patients in the benefit-risk assessment process? *Please provide reasons for your answer*

8) Can you suggest any possible solutions to overcoming these barriers? *Please provide reasons for your answer*

9) Has your organisation developed a model/method for communicating benefit-risk balance to patients? *Please comment or provide examples*

*If your organisation does not involve patient representatives, patient advocate groups or patients in benefit-risk assessment please answer question 10 and then go to Question 15 on Page 8.*

10) Does your organisation have any plans to incorporate patients into benefit-risk assessment? (Please comment or provide examples)

*Now go to Question 15*

*If your organisation does involve patient representatives, patient advocate groups or patients in benefit-risk assessment please answer questions 11-15:*

11) Who is involved? *Please circle all that apply*

Patient representatives	Patient Advocate Groups	Patients
-------------------------	-------------------------	----------

12) If what context are they involved?

13) What criteria do you use when selecting patient representatives/patient advocates/patients?

<p><i>Patient representatives / patient advocates:</i></p>  <p><i>Patients:</i></p>
---

14) How do you ensure the patient representatives/patient advocates/patients involved in the benefit-risk assessment of a new medicine are representative of the patients who will end up receiving the drug?

<p><i>Patient representatives / patient advocates:</i></p>  <p><i>Patients:</i></p>
---

15) Would you or another representative from your organisation be interested in taking part in a semi-structured interview about involving patients in benefit-risk assessment? *Please circle*

Yes	No
If yes, please provide contact details below:	
Name	
Telephone Number	
E-Mail Address	

16) Do you have any other comments?

*We are also collecting some limited demographic data to help with the analysis of this research. If you are happy to complete this information, please go to page 8*

DEMOGRAPHICS

*Please circle the relevant option*

What is your age group?	18-24	25-34	35-44	45-44	55-64	65-74	75-84	85+
How would you describe your ethnicity?								
How would you describe your gender?								
What is your highest level of education completed to date?	No school	High school	Trade / technical / vocational qualification	Bachelor's Degree	Master's Degree / Professional Degree	Doctorate Degree	Prefer not to answer	

*Many thanks for completing this questionnaire*

Benefit-risk assessment incorporating patient views

QUESTIONNAIRE for PATIENT REPRESENTATIVES and PATIENT ADVOCATE GROUPS (Survey PAG)

*Thank you for completing this questionnaire. The questionnaire should take approximately 15-20 minutes to complete.*

1) Which type of organisation are you involved with? *Please circle*

Patient Advocate Group	Charity	Other, please state:
------------------------	---------	----------------------

Name of organisation (optional)	
Job/Role Title (optional)	

Background Information

Before a new medicine is approved for marketing, evidence must be available to demonstrate the safety, quality and effect of the drug. A detailed assessment is completed using all available clinical trial data; to ensure the benefits of the product are carefully balanced against the risks. Benefit-risk assessment is a vital stage of the drug approval process and is an important task for regulatory agencies and pharmaceutical companies. There are a number of different methods used for benefit-risk assessment and different regulators and pharmaceutical companies use a variety of different ways. This sometimes involves developing a list of benefit and risk criteria (for example, a benefit could be 'less pain' and a risk could be 'increased side effects') and then ranking the criteria in order of importance. Involving patients in benefit-risk assessment is a new development. Patients, who are taking medications for their various conditions, may view benefits and risks very differently when compared with the views of pharmaceutical companies or regulatory assessors; however there has been limited research in this area. The aim of this questionnaire is to obtain your personal views on the matter.

2) Are you aware of any initiatives involving patients in the benefit-risk assessment of medicines? *Please comment*

3) Do you feel there is a need to incorporate patient views into benefit-risk assessment? *Please provide reasons for your answer.*

4) What is your personal opinion on the perceived benefits/positives of incorporating patient views in benefit-risk assessment? *Please provide reasons for your answer.*

5) What is your personal opinion on the perceived risks/negatives of incorporating patient views in benefit-risk assessment? *Please provide reasons for your answer.*

6) Would you or another representative from your organisation be interested in taking part in a semi-structured interview about involving patients in benefit-risk assessment? *Please circle*

Yes	No
If yes, please provide contact details below:	
Name	
Telephone Number	
E-Mail Address	

7) Do you have any other comments?

*We are also collecting some limited demographic data to help with the analysis of this research. If you are happy to complete this information, please go to page 4*



DEMOGRAPHICS

*Please circle the relevant option*

What is your age group?	18-24	25-34	35-44	45-44	55-64	65-74	75-84	85+
How would you describe your ethnicity?								
How would you describe your gender?								
What is your highest level of education completed to date?	No school	High school	Trade / technical / vocational qualification	Bachelor's Degree	Master's Degree / Professional Degree	Doctorate Degree	Prefer not to answer	

*Many thanks for completing this questionnaire*

### *Testing and validation of the surveys*

The draft Survey P-R was tested by an individual who had previously worked in B-R assessment within a pharmaceutical company. Feedback was received and this was incorporated into the final approved version. The tester commented on readability, understanding of the concepts involved and the flow of the survey.

The draft Survey PAG was tested by two patient representatives from the Guy's and St Thomas' patient advocacy group. They commented on the readability and also on the understanding of the concepts involved. Corrections were made to the final version based on the feedback received.

### *Cardiff University Ethics Application*

For the surveys, an ethics application was developed for submission to Cardiff School of Pharmaceutical Sciences Ethics Committee. The letter of approval is filed in Appendix VIII.

### *Activation of surveys on SurveyMonkey*

Once approved, the paper surveys were transcribed to *SurveyMonkey* where they were tested online. The individual who advised on the content of Survey P-R undertook a mock survey which was tested and validated. Once it was evident that the surveys were functioning as expected, they were activated on *SurveyMonkey* and recruitment could be commenced.

### *Recruitment*

Regulatory agencies, pharmaceutical companies, patient advocacy groups and patient charities were identified from Google searches and organisation's main contact email address were located. Various online groups related to B-R assessment on the social networking website *LinkedIn* were also searched for individuals involved in B-R assessment, and messages (using the REC approved template) were sent via the internal messaging system.

There is a consistent problem with obtaining key expert opinions due to the representativeness of sample populations. Against this background, investigation of small populations of expert opinion in particular, there can be ensuing confidence of surveying a sizable proportion of that population (Christopoulos, 2009). A number of expert professionals possess knowledge or can make assessments that are not available in the public domain. This knowledge is often considered confidential, sensitive or privileged (Christopoulos, 2009).

A snowballing approach was taken to recruitment, in that colleagues passed on details of the survey and further participants were identified from participants' existing networks.

#### *Descriptive statistics*

Once participants had completed the survey, and the survey was closed to recruitment, data was displayed using descriptive statistics. Centre weighted Likert scales were used for several questions in Survey P-R where participants could rate their level of agreement to various statements (Strongly agree, agree, neutral, disagree, strongly disagree), and participants were also given the opportunity to comment on the reasons for their answer. Their comments were used within the subsequent thematic analysis of qualitative data, to support the codes and eventual themes that were to be identified from the data set.

#### *Thematic analysis and generation of codes / themes*

Braun and Clarke (2013) described the stages of coding and analysis which make up thematic analysis. After the participants had answered the questions, it was important to read and to become familiar with the data, making note of items of potential interest. The next stage was to undertake coding, or organising the data into themes, before deciding upon which themes and sub-themes were prevalent across the dataset and which were of most importance. The themes identified would later be used to develop theory in phases II and III of the research study.

## **Results and thematic analysis**

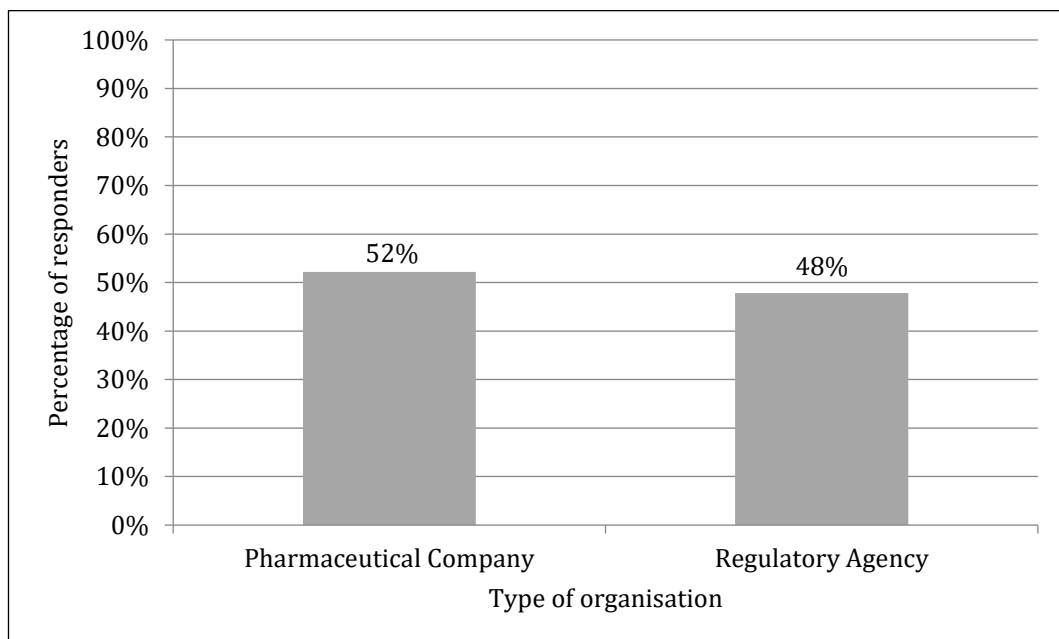
Braun and Clarke (2013) described how the results and thematic analysis sections of a qualitative report are often combined, as qualitative data analysis inevitably involves discussion of those data in order to be able analyse it appropriately. Therefore, the descriptive statistics are presented where applicable, however, as the majority of the dataset from the surveys was qualitative in nature, the thematic analyses were incorporated into a combined results and analysis section. The results from the two surveys were separated into two sections, though, the different perspectives were compared and contrasted as part of the thematic analysis.

During the analysis of the data collected during research phase I, the opportunity arose to submit the preliminary results to a conference. As such, a poster abstract was submitted to the UK Clinical Research Facility Conference (July 2015). Not only was the abstract accepted, the conference organisers requested an oral presentation as part of the conference's closing plenary session (Appendix III). After the success of the first submission, a second abstract was submitted to the European Conference of the Research Quality Association, Nice, France in April 2016. The poster abstract was also accepted (Appendix IV).

## Survey to regulatory agencies and pharmaceutical companies (Survey P-R)

Survey email requests were sent to 77 organisations (39 regulatory agencies and 38 pharmaceutical companies). Of the 36 individuals that responded positively and commenced the survey, 23 participants completed it in full and were therefore included within the analysis.

**Figure 4.1 - Type of organisation**



Question 1 of the survey asked participants about the type of organisation for whom they worked. It can be seen that just over half of participants (52%) worked for pharmaceutical companies and just under half (48%) worked for regulatory agencies. It was voluntary to answer Question 2, which requested the organisation's name. This was important to ensure that there were not multiple participants taking part from the same organisation which would have skewed the data. It was imperative to protect the confidentiality of participants; therefore, participants were given the opportunity to share their organisation's name if they felt comfortable to do so. Only those participants who consented to the sharing of this information have been included in Table 4.1.

**Table 4.1 – Participant’s organisations**

<b>Organisation</b>
<i>Regulatory agencies</i> <ul style="list-style-type: none"><li>• European Medicines Agency (EU)</li><li>• Federal Agency for Medicines and Health Products (Belgium)</li><li>• Health Sciences Authority (Singapore)</li><li>• State Agency of Medicines (Estonia)</li><li>• Therapeutic Goods Administration (Australia)</li></ul>
<i>Pharmaceutical companies</i> <ul style="list-style-type: none"><li>• GlaxoSmithKline</li><li>• Novartis</li><li>• Merck Serono</li></ul>

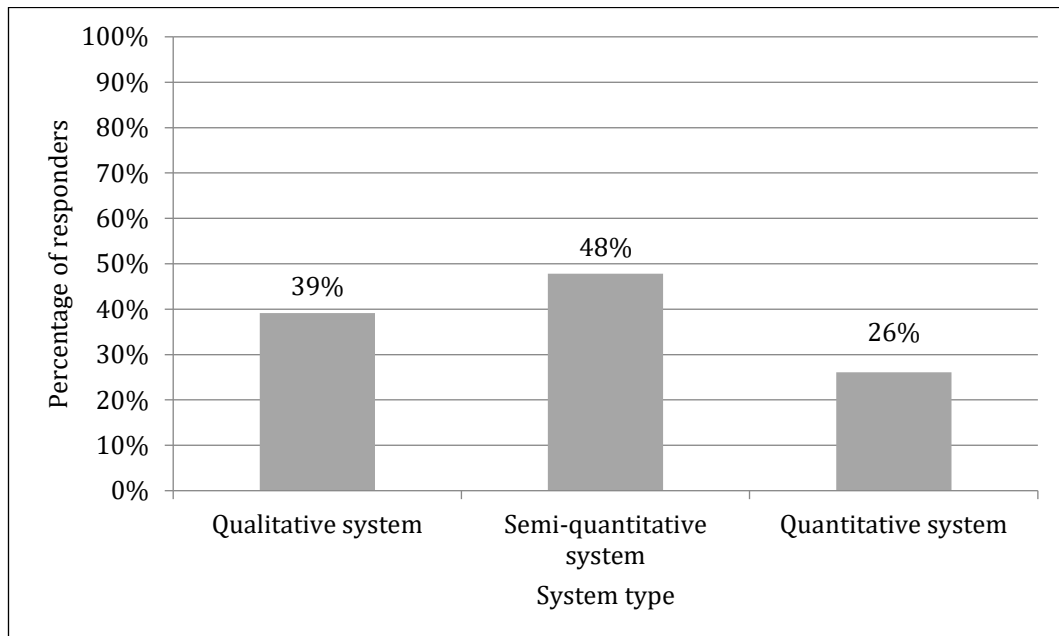
Question 3 was voluntary and inquired about the participant’s job title, position or role. It was crucial to protect the confidentiality of participants; therefore, only those participants who consented to the sharing of this information have been included in Table 4.2.

**Table 4.2 – Participant’s job title / position / role**

<b>Job title / position / role</b>
<i>Regulatory agencies</i> <ul style="list-style-type: none"><li>• Senior Regulatory Specialist</li><li>• Head of Bureau of Pharmacovigilance</li><li>• Member, Advisory Committee of Pharmacovigilance</li><li>• Clinical Epidemiologist</li></ul>
<i>Pharmaceutical companies</i> <ul style="list-style-type: none"><li>• Senior Director, Benefit-Risk Evaluation</li><li>• Medical Director, Global Drug Safety Medicine</li><li>• Drug Safety Product Lead</li><li>• Chief Medical Officer</li><li>• Medical Writer</li><li>• Statistical Methodologist (Benefit-Risk)</li></ul>

Question 4 asked participants which of the following best described the system used to undertake their B-R assessment: qualitative, semi-quantitative or quantitative and the data obtained is displayed in Figure 4.2.

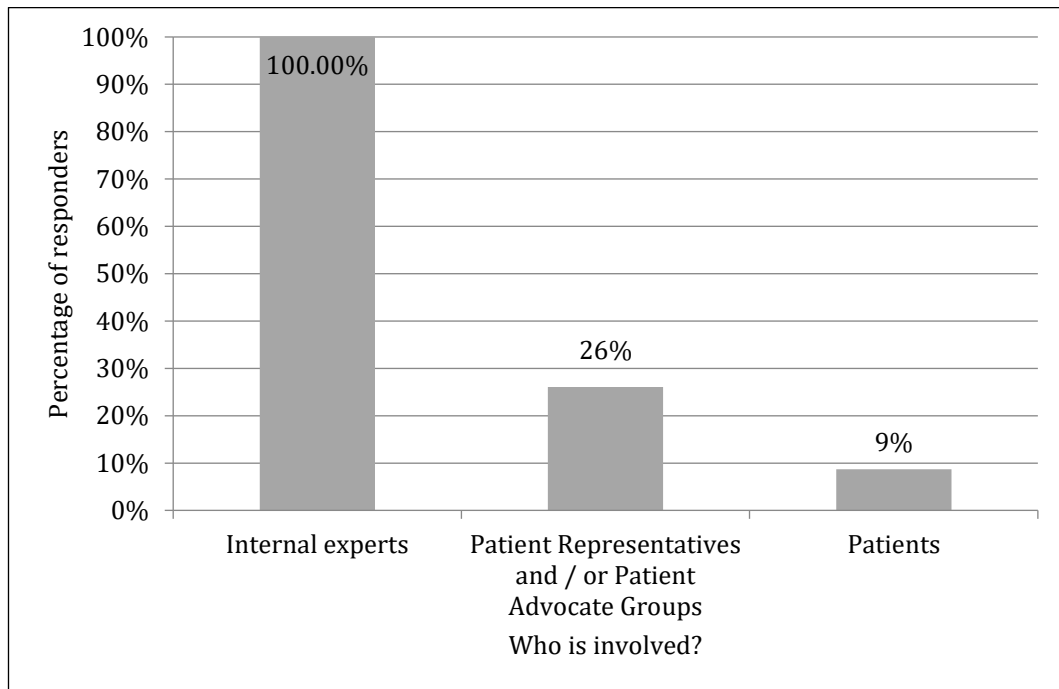
**Figure 4.2 – Type of system used by organisation**



Interestingly, as shown in the literature, the majority used a semi-quantitative system, though, there remained examples of both fully qualitative and fully quantitative still in use by both regulatory agencies and pharmaceutical companies.

Question 4 asked participants which individuals within the organisation were involved in B-R assessment and analysis.

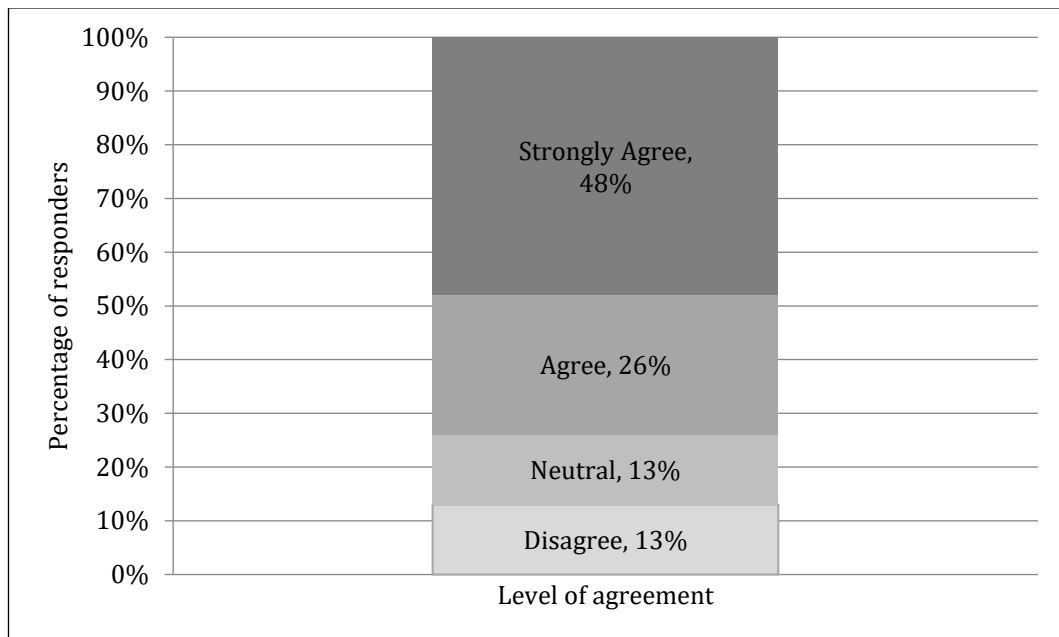
**Figure 4.3 – Individuals involved in B-R assessment within the organisation**



All participants stated that their organisations had internal experts who participated in B-R assessment. However, just over a quarter of organisations (26%) involved patient advocacy groups or patient representatives. Only 9% involved patients at the time of undertaking the survey.



**Figure 4.4 – Participants’ level of agreement on incorporating the views of patient representatives and/or patient advocate groups into benefit-risk analysis**



Question 6/7 surveyed the participants’ level of agreement with this statement, as well providing the opportunity to give reasons for their opinion as shown in Figure 4.4. The majority of participants (74%) agreed that patients should be involved in B-R assessment, however, several participants stressed the challenges which must be overcome.

*Strongly agree*

Participants who strongly agreed had similar opinions as to why patient advocates should be included in B-R assessment. For example, **Participant 03** stated that ‘It’s important to understand which endpoints are important to patients.’ This is vital and it highlights the need for ‘insight into the patient experience’.

**Participant 07** emphasised how patients view conditions differently to regulators when they stated that ‘I do support patient's involvement as risks (side effects) can be differently be judged by them than in the expert's opinion. For example, alopecia is clinically less severe than myelosuppression, but a patient may feel the reverse. This situation can be reflected (statistically) in benefit-risk tools weighting efficacy and any single side effect’ This also supports the emerging theme of ‘insight into the patient's experience.’

**Participant 10** highlighted that ‘patients and caregivers views are crucial in helping us to understand the wide definitions of benefit and risk from the point of views of those who receive the treatment with or without choice of other treatment options.’ This was supported by **Participant 17** who stated that ‘patient's subjective views on benefit-risk tradeoffs are a prerequisite to making a decision that is for their best interests.’

**Participant 22** was the first to underscore the role of patients in ‘enhancing decision-making’ when they stated that patient involvement ‘adds robustness to decision-making, and to consider various perspectives to make a relevant decision that matters to the patients and their healthcare. Increasingly it is difficult to act as proxies for patients in regulatory decision-making, and it is better to engage their views directly.’

*Agree*

**Participant 04** stated that ‘it needs to be more than simply participating, they need to be part of decision.’ This is interesting as it draws attention to another emerging theme of ‘equality’ and how all stakeholders should perhaps have equal rights within the process.

**Participant 09** stated that the ‘patient receives the medicine and own the experience. Their view points are therefore vital. If they can be fed through a group/rep that is great, however that person would be a filter which I personally would prefer to avoid.’ This is an interesting perspective as this was the exact reasoning behind the structure of the survey, separating patient

representatives and patient advocates from patients. This participant understood the difference between these two groups whereas other participants perhaps did not. The use of the term 'filter' shows up this difference perfectly. The patient's experience becomes less when it is seen through the eyes of another and presented by someone who did not 'live the experience.'

**Participant 19** stated that 'without a doubt, all stakeholders should have a hearing but not all stakeholders should carry equal weight. Desperate patients may have one view which would be, arguably, contrary to the public health view for example.' This is the opposing view of **Participant 04** who, although they both agreed that patient representatives should be involved, they disagreed on the imposition of equal rights within decision-making.

#### *Neutral*

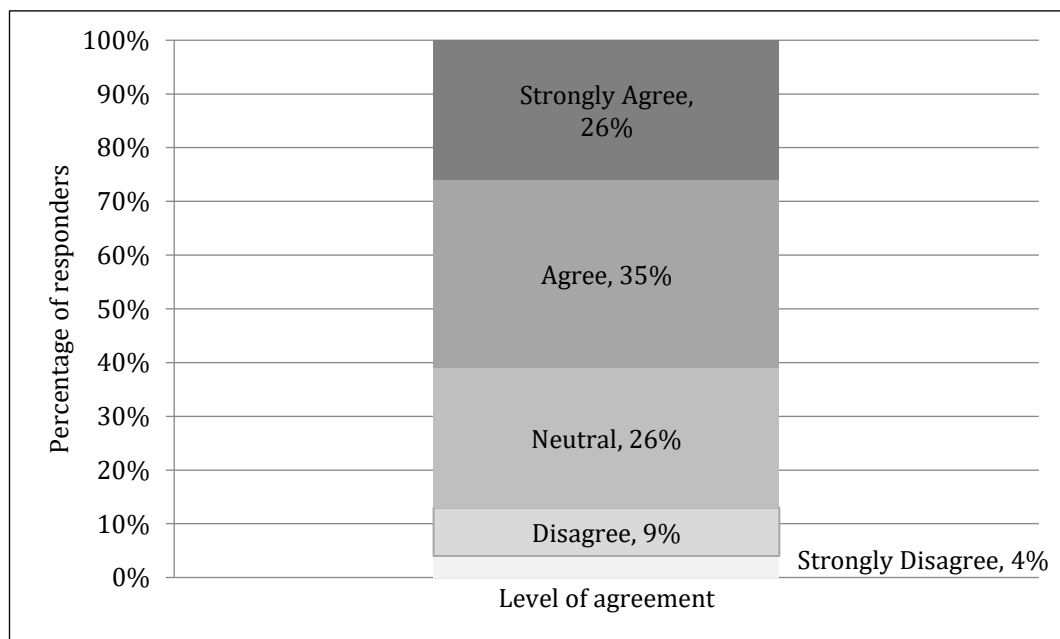
More participants took a neutral stance on this question, indicating that the patient representatives' involvement in benefit-risk decision-making was less acceptable than the actual participation in B-R assessment. This is an important distinction. **Participant 06** stated that 'the patient's view should be evaluated for setting up a study as this might increase the compliance with the study cons for such a procedure may be the lack of time or making the process more complex; [...] the input/feedback from patients can be dependent on their educational background.' This highlights an emerging theme of 'understanding, training and education.' **Participant 08** stated that 'patients and patient groups can be different sets of people. I believe both need to be involved in information give and take and decision-making, and this should be done in the context of the same principles of shared information and shared goals as the other stakeholders involved.'

**Participant 12** highlighted that the ‘analysis should be objective, patient views likely to be subjective. In principal it could be a good idea to consult patients on some matters for example what kind of risk they consider acceptable/unacceptable.’ The objectivity of patients is a challenge raised by participants which must be addressed.

*Disagree*

**Participant 01** indicated how ‘patients are able to provide clear insight into patient reported outcomes and endpoints that can be utilised for this purpose.’ This indicates that this participant did not feel that increased patient involvement, other than via the use of PROMS, was required. This opinion was not in line with the opinions of the majority.

**Figure 4.5 - Participants’ level of agreement on incorporating the views of patient representatives and/or patient advocate groups into benefit-risk evaluation and decision-making**



Question 8/9 surveyed the participants’ level of agreement with this statement, as well as imparting the opportunity to give reasons for their opinion as shown in Figure 4.5.

The majority of participants (61%) agreed that patients should be involved in B-R evaluation and decision-making, however this outcome was markedly lower than the previous question about their general involvement (decrease of 17%). Again, several participants highlighted the challenges which must be overcome.

*Strongly agree*

**Participant 02** stated that 'they have an overview of patient needs,' indicating that this participant felt that patient representatives do in fact reflect the needs of patients. **Participant 18** asserted that 'democracy' was important, as was 'the respect of all stakeholders.' These indicated themes of 'insight into the patient's experience,' 'democracy' and 'equality' which have emerged from the data so far.

*Agree*

**Participant 07** thought that 'voting rights can only be done in collaboration with regulatory agencies e.g. for submission purposes, marketed products. During development, the decision-making bodies are within the company driven by their goals.' **Participant 09** stated that 'It depends on the decision, if it's based on whether the risk outweighs the benefit and therefore the medicine is removed from market - no. Patients for the most part will focus subjectively and on themselves, not considering the patient population as whole.' **Participant 10** believed that 'the decision-making process should ensure the input if patients groups is not neglected. To involve them in discussion is one, but to take their wish list into account is another.' This again underscores the concern that patients may not be objective. The use the term 'their wish list' is interesting, as it has negative connotations, for example, suggesting the patient may have ulterior motives. An emerging theme of 'motives' appeared when coding this dataset.

*Neutral*

**Participant 03** stated that 'I think it depends: some regulatory decisions will depend on benefit-risk (where patient input is important); some may depend on other issues (e.g. stability of the product) where the patient input may be less relevant.' **Participant 19** stated that 'I'd insist on transparency regarding the representatives. My long-term experience has made me rather cynical and many stakeholders have secondary and even tertiary agendas which are not always consistent with the best outcome for patients and public health.' This supports the emerging theme of 'motives' as it also indicates that stakeholders, including patient representatives and perhaps even patients, have ulterior motives. This is an important theme to highlight. **Participant 21** stated that 'this is interesting. I've [heard] about being influenced by patient group assessments of the impact of risks, and I am aware that patient advocacy groups attend FDA advisory committee meetings, but I had never considered the possibility of regulatory bodies and patient advocacy groups forging an official collaboration for aspects of the decision whether to approve.' This was interesting as this participant was not aware of the official collaborations which were developing within this field.

**Participant 22** stated that 'for patients and advocacy groups to make a meaningful contribution, they must first understand the regulatory processes, our basis of decision-making and the full implication of their decision. Thus, I believe with time and effort from regulators to educate the patients, we can look forward to incorporating patients views in an official approach like voting.' This was the first evidence of the emerging theme of 'understanding based on education' which was an important concern for several participants.

*Disagree*

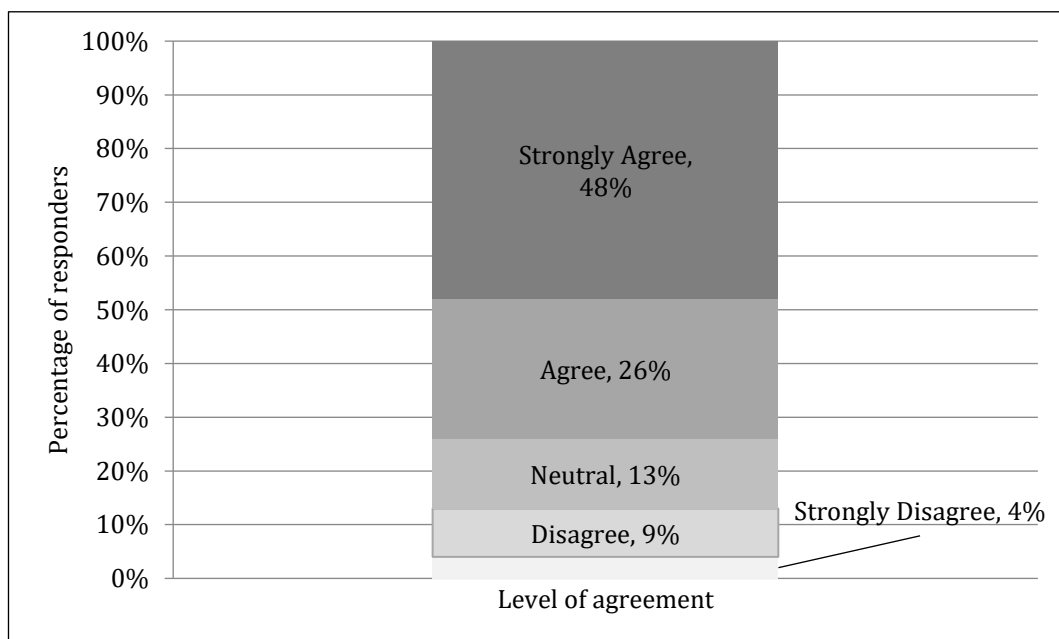
**Participant 06** stated that 'if there is no established procedure I would refrain from inclusion of the patient representatives.' The lack of an established process for involving patients directly was a concern, and one which will be addressed by this thesis.

**Participant 11** stated that ‘patients should not be empowered. Their views are valued, but nothing more than that. Furthermore, in case patients are allowed a vote, who is to blame if the decision is wrong?’ This is a valid concern, as responsibility is an important aspect of regulatory decision-making, although, to suggest that patients should not be empowered is an unacceptable position. Patient empowerment within the management of their own condition is essential to improve health and reduce overall healthcare costs. This is a given.

*Strongly disagree*

**Participant 12** stated that ‘the assessment should be data driven.’ This participant’s previous position about involving patient representatives and patient advocates was neutral. It was therefore first assumed that this participant came from a fully quantitative background based on these comments. However, on checking their previous responses, they used a semi-quantitative approach to B-R assessment, so this position conflicted with their opinion on involving patient representatives.

**Figure 4.6 - Participants’ level of agreement on incorporating the views of patients into benefit-risk analysis**



Question 10/11 surveyed the participants' level of agreement with this statement, as well as affording them the opportunity to give reasons for their opinion, as shown in Figure 4.6. The majority of participants (74%) agreed that patients should be involved in B-R assessment, an identical value to Question 6/7 about involving patient representatives and patient advocates. However, as with previous responses, several participants disclosed the challenges which must be overcome.

#### *Strongly agree*

**Participant 09** responded that 'the patient owns the experience and with unfiltered voice, they can have a powerful message.' They used the term 'filter' for the second time, to refer to the relationship between patient representatives/patient advocates and patients.

**Participant 17** stated that 'patient's subjective views on benefit-risk tradeoffs are a prerequisite to making a decision that is for their best interests.' This is interesting as the participant may have been noting that patients are not objective and was accentuating their subjectivity as a positive element rather than a negative one.

**Participant 21** stated that 'I have not pondered the distinction between direct patient representation and patient representation via advocacy groups.' Again, this was noted from the dataset whereas some participants saw patient representatives and patient advocates as the same as patients.

#### *Neutral*

**Participant 15** stated that 'it is difficult to provide complex information, in ways that can be properly understood.' This is another example of the emerging theme of 'understanding.' In addition, **Participant 22** also used the term 'filter' when describing patient advocates, however, this time it was used positively. They stated that 'representatives or advocacy groups may be useful to filter the unnecessary emotions behind the opinions, and also allow a collation of views to make the opinions more moderated and fair.'

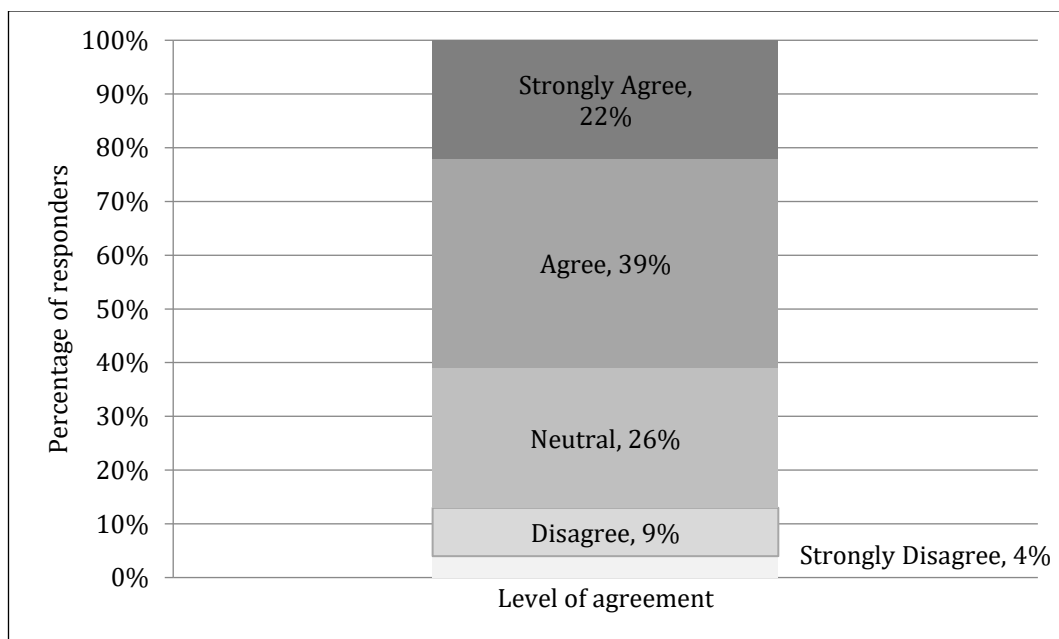


This links in with the patient’s objectively so it is an interesting point and reflects the other side of the argument.

*Disagree*

**Participant 12** again reaffirmed that ‘information from patients could be taken into account but the analysis should be made by specialists and be data driven.’

**Figure 4.7 - Participants’ level of agreement on incorporating the views of patients into benefit-risk evaluation and decision-making**



Question 12/13 surveyed the participants’ level of agreement with this statement, as well as affording them the opportunity to provide reasons for their opinion, as shown in Figure 4.7. The majority of participants (61%) agreed that patients should be involved in B-R evaluation and decision-making, however this response level was markedly lower than the previous question about their general involvement (decrease of 17%). Again, several participants highlighted the challenges which must be overcome.

### *Agree*

**Participant 09** stated that 'I agree because the decision pendulum swings both ways, patients could provide compelling testimony to keep a drug on market which they feel is worth the risk. Quantitatively it may not be.' This is important as they affirm that just because something may not be data driven, does not mean it isn't important. They also declared that 'on the flip side, patients consider their experience the only experience and therefore be biased.' This participant also maintains that patients may not be objective and can also have an inherent bias, like all stakeholders involved. However, the statement that they consider 'their own experience the only experience' is perhaps unfair and unlikely to be true. Many patients participate in clinical trials to help society and for 'the greater good' therefore patients most definitely do consider the needs of others.

**Participant 10** indicated that patient inclusion in decision-making should 'depend on the conditions (e.g. cognition issues, terminal state etc.), patients may be unable to exercise their rights, hence their caregivers should always be able to stand in for them. The difficulty would present on the incorporation of this into national laws and regulations.' The fact that caregivers should be included is also another consideration within the process. **Participant 13** pronounced that 'there are instances where questions have been posed that have changed policy, advocated by the consumer representative alone.' This highlights the impact some patient representatives previously had on decision-making. Their unique insight affected policy change which is important.

### *Neutral*

**Participant 15** communicated that it is 'difficult to provide appropriate information,' referring to the data which should be presented to patients. This is a challenge that must be raised and addressed. The exact technique of presenting clinical trial data to patients in a way in which they understand was an emerging theme within the dataset.

**Participant 16** was clear in their reasoning for a neutral stance to this question. They stated that ‘incorporate their view, yes. Voting, not so sure. This may be biased.’ This indicated that the participant was concerned that there was a risk that patients would not remain objective, a common emerging theme within the dataset.

#### *Disagree*

**Participant 06** reiterated their view that ‘if there is no ‘validated’ process how to deal with such a voting, I would refrain from this’ indicating that the methods of patient inclusion is an important emerging theme.

#### *Strongly disagree*

**Participant 12** stated that the ‘decision should be data driven and objective, patient views likely to be subjective.’ The patient’s objectivity in decision-making was again called into question by this participant.

#### *The perceived benefits of incorporating patient views in B-R assessment*

Question 14 invited participants to draw attention to the perceived benefits of incorporating patients in B-R assessment. **Participant 04** replied that ‘we develop drugs to address unmet patient needs, they are central to defining the benefit-risk proposition, should be closely involved and vote on the matter, the challenge will be to ensure the correct patient representation and training so they are on an equal footing.’ This participant also highlighted several emerging themes: insight, democracy, equality, understanding, education and also the difference between patient representatives/advocates and patients.

**Participant 09** specified that the following are benefits of patient inclusion: ‘understanding of the medicine in real life settings, unfiltered experience report, real time feedback.’ **Participant 10** highlighted that in some situations, the patient’s perspective is a necessity, when they stated that ‘in case such as orphan diseases, benefit-risk assessment can be a matter of one person or a few individuals and no assessment model can replace the individual personal assessment.’

Moreover, **Participant 11** noted that ‘patients may be less risk averse than regulators. Thus, in situations where the benefit-risk balance is uncertain, their input would be of value.’ Risk communication was a common point throughout the literature, therefore this is a key point. In addition, **Participant 12** acknowledge the theme of ‘insight’ when they stated that ‘patient views could give more insight in the risks that are acceptable to patients.’

**Participant 19** identified that patient involvement would be ‘marginally useful for major diseases that are well characterized and understood by the companies, regulators and physicians. More useful and often very valuable for orphan diseases or strange forms of more common diseases. Having lived through some of the RU486 (Mifepristone) debates some years ago, this became political, social and religious far more than medical. I see virtue where the issue is not too political (new anemia treatment perhaps) rather than on the controversial issues (psychiatric, abortion, Ebola etc.) where the decision is often made by others than the direct stakeholders.’ This is interesting as IMI-PROTECT also disclosed that the patient’s perspective may in fact be most valuable for orphan diseases.

**Participant 21** stated that ‘the overall science of drug development will improve as a result of patient views being incorporated into benefit-risk assessments. I believe it will help improve trial designs (choosing endpoints that matter most to patients). I believe it will improve the quality of signal detection (since the severity/impact of a risk on patients can play an iterative role in the holistic safety assessment of an emerging drug).’ This was an interesting perspective, as this was the first time that signal detection was mentioned.

**Participant 23** indicated ‘that users’ views are taken into consideration - so that the level of risk individuals are willing to take and the level of benefit patients are seeking is considered. The decision-making will be more balanced with this "holistic" view.’

*The perceived risks / negatives of incorporating patient views in B-R assessment*

Question 15 asked participants to focus on the perceived risks or negatives of incorporating patients in B-R assessment. **Participant 02** signified that ‘the methodology for eliciting patient preferences was developed in other fields, and it not well enough understood how well these methods work in a medical context.’ What is more, **Participant 04** specified that ‘incorrect training, and politicisation of the process’ could result from patient participation, ‘where opinions matter more than science.’

**Participant 05** stated that patients may have the ‘inability to understand the concepts of risk and harm.’ Whilst **Participant 06** declared that there is ‘no "monetary value" for a company’ which was the first-time financial aspects had been raised by a participant. This was supported by **Participant 07** who stated that ‘companies are private institutions and [...] carry the full financial risk during development,’ therefore increased costs are a concern for industry. **Participant 06** also noted that ‘patient aspects might not reflect the overall value but may be very individual and therefore not ‘neutral.’ **Participant 09** supported the emerging theme of ‘motivation and ulterior motives’ as they could present ‘self-serving opinions’ as this is ‘human nature.’ They also commented that the opinions may be subjective rather than objective.

**Participant 10** highlighted that patients may not be representative. They stated that ‘the risk is the difficulty in ensuring ethical issues are addressed when it comes to those who are not able to speak for themselves (e.g., terminal patients etc.), you would need a very efficient way of ensuring the right people are being listened to. Hence, an implementation problem.’ The second aspect of the statement also touched on the selection of patients which is another methodological issue. **Participant 11** also touched upon this when they stated that ‘it may be very difficult to involve patients. The obvious question is who, how and when?’

**Participant 13** flagged up the theme of ‘understanding’ when they denoted that ‘this depends on a willingness of the consumer working to understand the complex issues under discussion and appreciating the limits of the role.’

**Participant 15** also raised the issue of ‘understanding’ when they highlighted that a risk could be ‘providing information that can be appropriately understood.’ Additionally, **Participant 16** raised the issue of objectivity when they stated that ‘patients views maybe biased, especially in case media interest is involved.’ This was the first example of where the media was mentioned yet it is a valid and interesting point for consideration. There were examples in the literature around risk communication which pinpointed the challenge of adequately communicating risk without sensationalising it.

**Participant 19** also mentioned financial challenges when they responded that ‘money, politics and secondary agendas will overcome the medical and public health aspects.’ The term ‘secondary agendas’ was interesting and it supports the emerging theme of ‘motivations of stakeholders.’

**Participant 20** emphasised the topic of objectivity when they stated that patients ‘may provide too emotional comments’ [*sic*]. **Participant 22** also unveiled the issue of subjectivity in that ‘there potentially introduces more subjectivity into this process of decision-making. As fast as the medical science evolves, patient’s views do change accordingly and their contribution must take into account of this as well. Typically, patients’ views are more affected by many social and cultural influences as compared to the scientific rigor established in a good benefit-risk assessment.’

#### *The barriers to involving patient views in B-R assessment*

Participants were able to suggest a range of potential barriers to involving patients in B-R assessment. Many focused on the emerging theme of ‘adequate methods for including patients.’ In this context, **Participant 01** replied that the ‘methodology of obtaining patient views for the incorporation of benefit-risk assessments’ is a barrier.

**Participant 02** had a similar opinion when they stated that ‘structural and logistical challenges in doing something new.’ They also commented that a ‘lack of internal expertise in preference elicitation methods and application’ is a barrier. **Participant 03** also mentioned that a ‘lack of established best-practice on how to do this.’ **Participant 05** stated that ‘better methods to capture patient input and creating a regulatory pathway to incorporate it.’

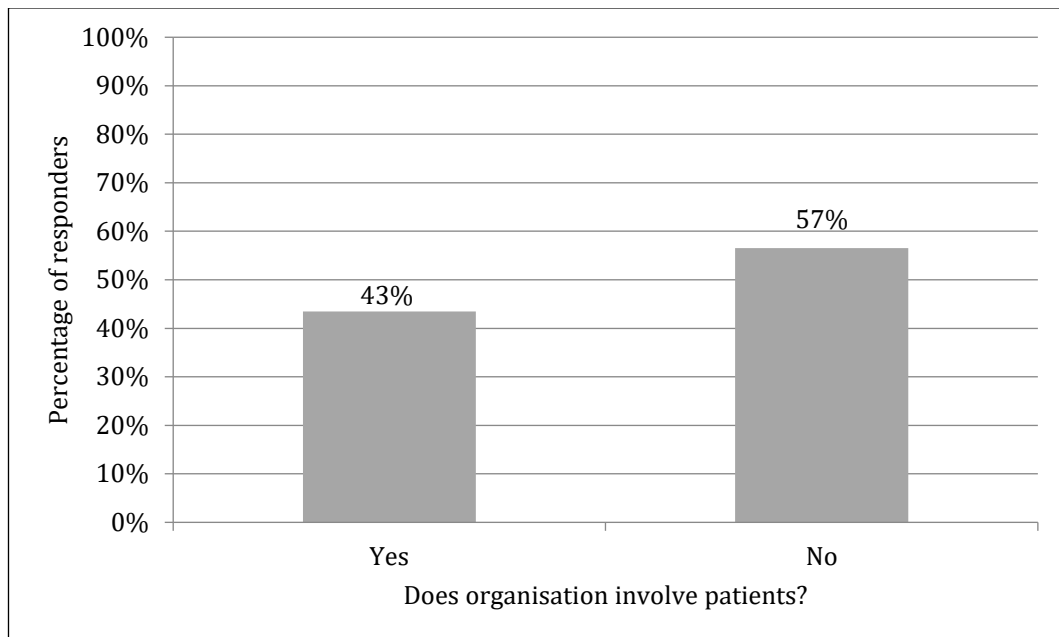
Patient representation was also a strong emerging theme. **Participants 05, 06 and 07** also commented on patient selection. **Participant 13** mentioned patient selection but commented from an educational perspective, in that ‘health literacy’ is important. Furthermore, **Participant 15** listed several barriers: ‘complexity of information, health and scientific literacy and interest groups/lobbies with pre-existing agenda.’ The latter was yet another example of ‘motivation and ulterior motives.’

**Participant 17** raised the potential ‘arrogance of some physicians’ which, in combination with **Participant 13’s** comment about the ‘the daunting nature of the social interactions of the committee work’ highlights a potentially emerging theme of ‘strong personalities.’ In light of this, **Participant 19** listed the following challenges: ‘language, sophistication, emotion, medical and public health awareness, quantitative thinking (how many know the difference between absolute and relative risk for example).’

#### *Possible solutions to these barriers*

Question 17 asked participants to comment on possible solutions to the barrier that they reported in their answer to question 16. Solutions included ‘improved training of experts’ (**Participant 01**), ‘training and broad representation’ (**Participant 04**), ‘development of a structured methodology and the inclusion of patients in licensing activities’ (**Participant 09**), ‘stronger, more active patient organisations’ (**Participant 16**), ‘improved transparency’ (**Participant 19**) and ‘potential use of social media to mobilise patient views’ (**Participant 21**).

**Figure 4.8 - Organisation's current involvement of patient representatives, patient advocate groups or patients in benefit-risk assessment**

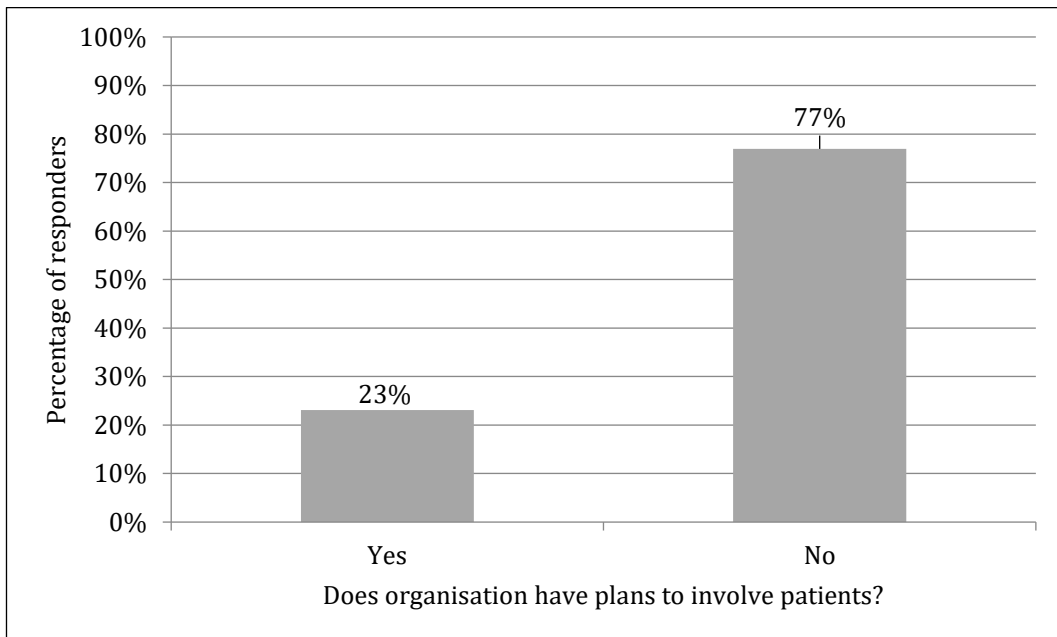


Questions 20 surveyed participants about the current involvement of patient representatives, advocates and patients in B-R assessment within their organisations and the data is displayed in Figure 4.8.

Ten participants confirmed that they were aware of initiatives within their organisations and continued to answer the remaining questions, displayed in Figures 4.9 and 4.10.

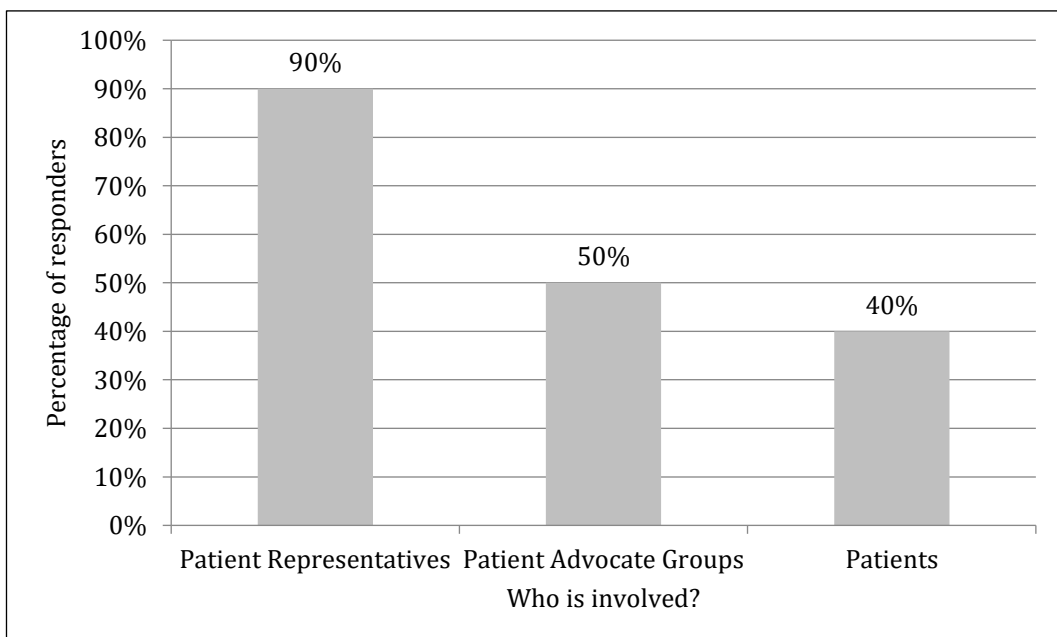


**Figure 4.9 – Participant’s knowledge of future plans to incorporate patients into benefit-risk assessment within their organisation**



Of the ten organisation that were aware of future initiatives, the range of stakeholders involved varied as shown in Figure 4.10.

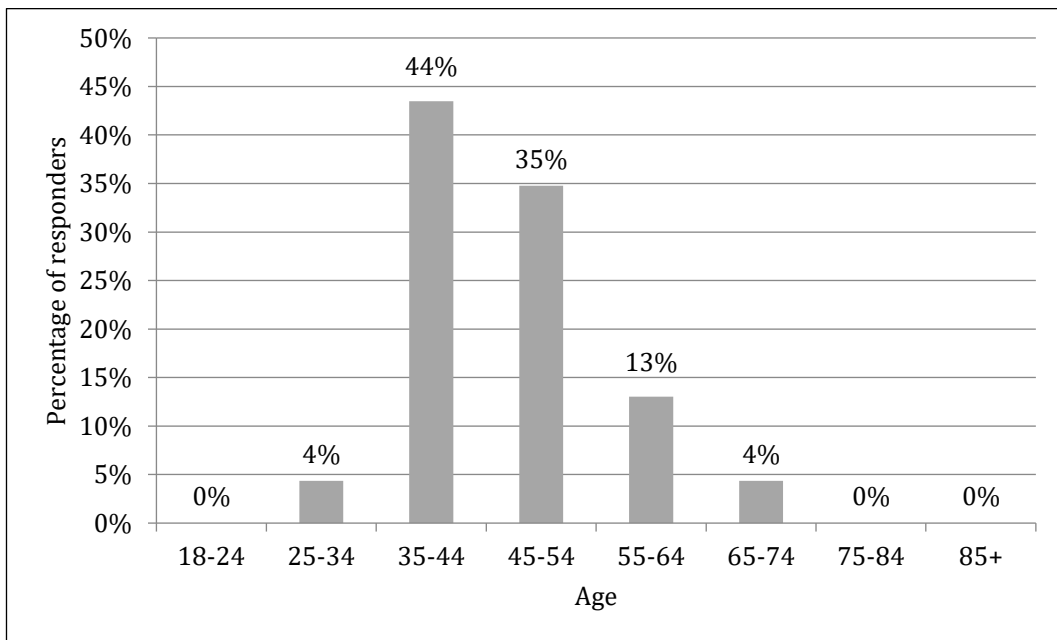
**Figure 4.10 – Types of stakeholder involved in initiatives involving patients in benefit-risk assessment within their organisation**



It was anticipated during the development of this research element that themes such as 'education,' 'understanding' and 'equality' may arise. Therefore, it was deemed important to collect some demographic characteristics from participants which may have been of use during the analysis of the research.

*Demographic characteristics of study participants*

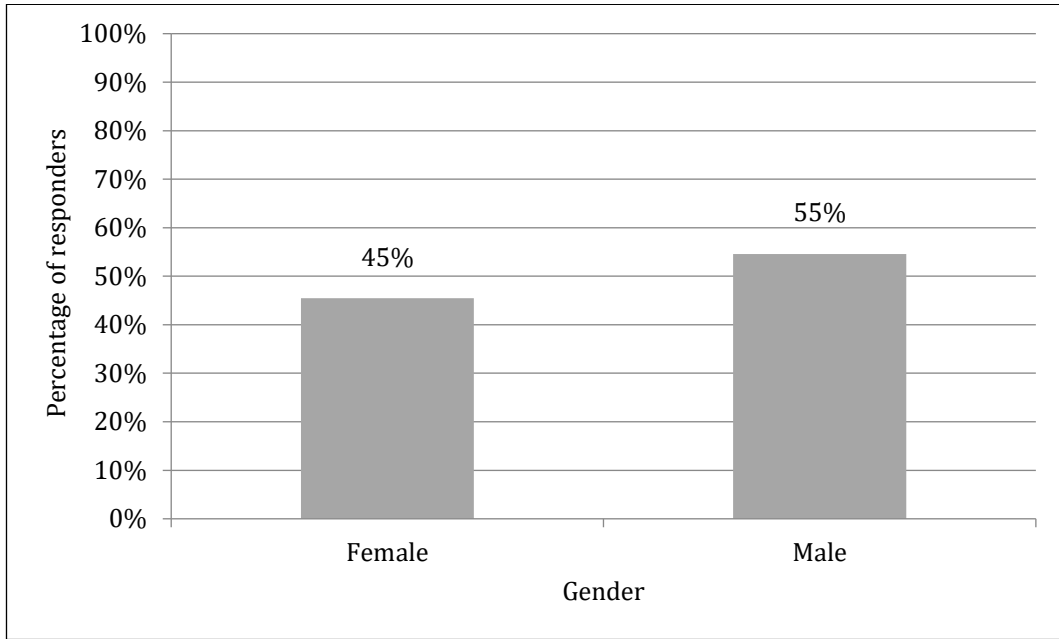
**Figure 4.11 – Age range of participants who completed Survey P-R**



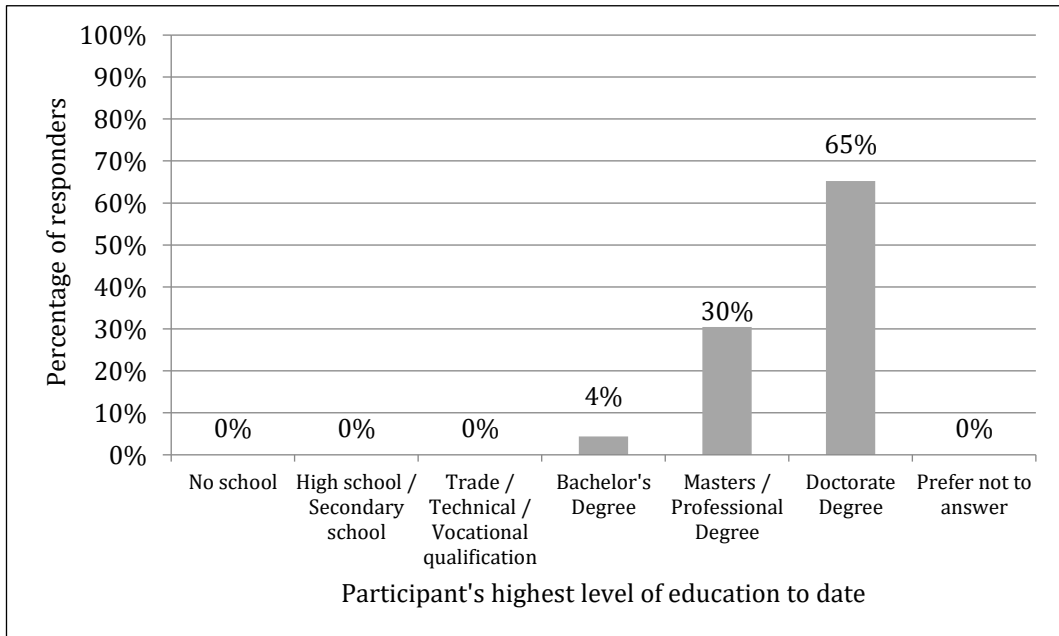
**Ethnicity of participants who completed Survey P-R**

When asked to describe their ethnicity, 1 person described themselves as 'Chinese' and all other participants stated they were 'Caucasian' (n=19). Three participants chose not to answer.

**Figure 4.12 – Gender of participants who completed Survey P-R**



**Figure 4.13 – Highest level of education of participants who completed Survey P-R**

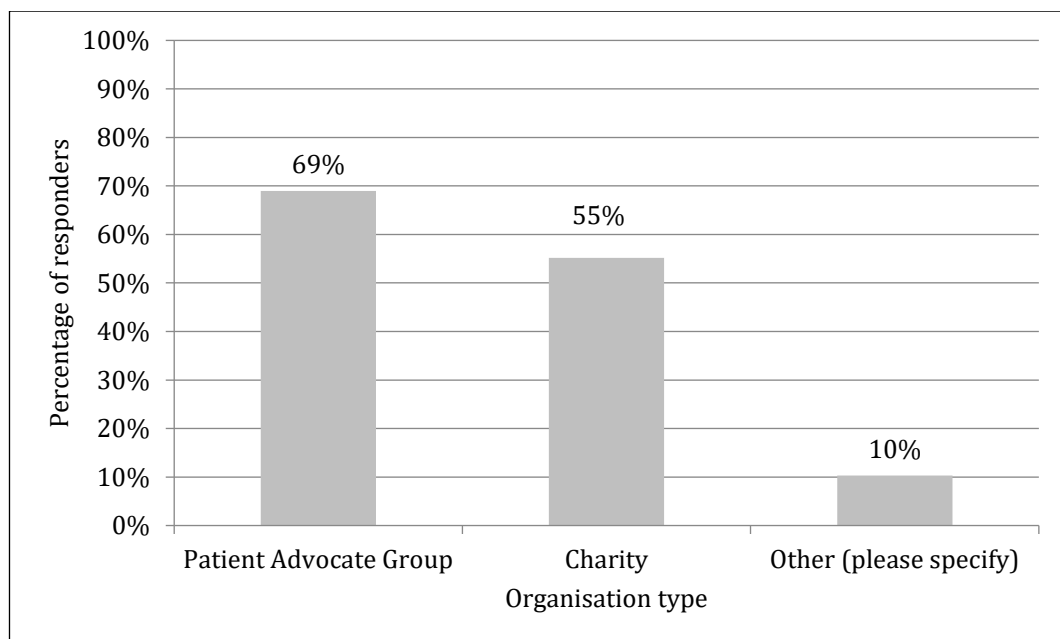


## Chapter IV (II) – Survey to patient advocacy groups, described as ‘Survey PAG’

Survey email requests were sent to 192 organisations. Of the 46 individuals that responded positively and commenced the survey, 29 participants completed it in full and were therefore included within the analysis.

It should be noted that participants were asked to ‘tick all that apply’ to question 1 about their organisation type, as some organisations described themselves as both ‘patient advocacy groups’ and they may also have been identified as ‘charities’, hence, the total value of all groups combined exceeds 100%.

**Figure 4.14 – Type of organisation (Survey PAG)**



Question 2 was voluntary and asked for the organisation name. This was important to ensure that there were not multiple participants taking part from the same organisation which would have skewed the data.

It was important to protect the confidentiality of participants; therefore, participants were given the opportunity to share their organisation name.

Only those participants who consented to the sharing of this information have been included in Table 4.3.

**Table 4.3 – Participant’s job title / position / role**

<b>Organisation</b>
<p><i>Patient advocacy groups and charities</i></p> <ul style="list-style-type: none"> <li>• NF Kinder Swiss "Positivrat" for HIV and HCV patient</li> <li>• Myeloma UK</li> <li>• Urostomy Association</li> <li>• British Liver Trust</li> <li>• Histamine Intolerance Awareness</li> <li>• SJS Awareness UK</li> <li>• Stevens Johnson Syndrome Awareness UK</li> <li>• Fibromyalgia Association UK</li> <li>• Epilepsy Society</li> <li>• Lupus Patients Understanding &amp; Support (LUPUS)</li> <li>• National Ankylosing Spondylitis Society (NASS)</li> <li>• HIV/AIDS Carers &amp; Family Service Provider Scotland</li> <li>• Polycystic Kidney Disease Charity</li> <li>• PNH Support</li> <li>• British Kidney Patient Association</li> <li>• FOFLEKKREFTFORENINGEN Norway</li> <li>• HTAP Belgique</li> </ul>

Question 3 was voluntary and asked for the participant’s job title / position / role. It was important to protect the confidentiality of participants; therefore, participants were the given the opportunity to share their job title / position / role. Only those participants who consented to the sharing of this information have been included in Table 4.4.

**Table 4.4 – Examples of participant’s job title / position / role**

<b>Job title / position / role</b>
<ul style="list-style-type: none"><li>• Board member</li><li>• Director</li><li>• CEO</li><li>• Chair of Trustees</li><li>• Chief Executive</li><li>• Coordinator</li><li>• Epilepsy Information Manager</li><li>• Founder / Head of organisation</li><li>• Health Services Research Manager</li><li>• Information and Communications Manager</li><li>• Involvement coordinator</li><li>• National Secretary</li><li>• Patient</li><li>• Policy Director</li><li>• President</li><li>• Senior Policy Advisor</li><li>• Trustee</li><li>• Vice president</li><li>• Visiting Researcher</li><li>• Volunteer</li></ul>

Question 4 surveyed participants on if they know of any initiatives about involving patients in the B-R assessment of medicines. The majority of participants were unaware of any initiatives and for most, this was the first time they had come across the concept of patient involvement in B-R assessment. Three participants, however, mentioned the EUPATI initiative and some were actually a member and had actively participated in the development of this project. Three also mentioned the EMA.

**Participant 08** had an interesting perspective when they stated that ‘NICE uses lay members to offer commentary and advice in its technology assessments and guideline development work, also the MHRA have a patient group which looks at devices and medicines from a safety viewpoint; the EMA regularly contacts us to link them with patients with a particular condition who can comment on a new medicine.’ This participant had a noteworthy viewpoint on the subject of B-R. The most knowledgeable participant, however stated that the ‘IMI work package due to start soon, which is a multi-stakeholder collaborative program examining this topic. EMA and FDA initiatives in this area are also underway. Myeloma UK is also undertaking collaborative projects in this field’ (**Participant 26**).

*The need to involve patients in B-R assessment*

When participants were surveyed about the whether they felt that patients should be involved in B-R assessment, 100% of the 29 participants who completed the survey agreed that they should be. **Participant 01** was positive and commented that they should be involved ‘especially for rare diseases without any treatment.’

**Participant 11** affirmed that ‘patient empowerment is important in all areas of medical care. Empowered patients are demonstrated to be more compliant with their treatment regimes. Exclusion of this user group from any point of the evaluation is a waste of resource.’ This is an interesting perspective when compared to that of **Participant 11 (Survey P-R)** who did not agree that patients should be empowered. **Participant 14** also added that ‘I think involving patients is important and necessary. There is little point in developing an ‘intervention’ if it is intolerable to the patient and patients are usually the best individuals to know what is an appropriate balance of risk and benefit.’ The last statement, in particular, demonstrates the risk that some patients may overstep the mark with regards to patient empowerment, which is possibly the exact point that **Participant 11 (Survey P-R)** was warning against.

It is argued that clinicians and regulatory scientists are the 'best people' to undertake this assessment, of course, in collaboration with other stakeholders.

**Participant 21** had strong opinions on this matter, which supports the development of the emerging theme around 'strong personalities' which may take the discussion away from healthcare and politicise it. They stated that 'a lot of information on the internet is highly speculative, spiked with personal opinion and sometimes patients are targeted by drug companies who attempt to sell products promising them that this is "the solution" to their problem.' This appeared to demonstrate a cynical view of pharmaceutical companies which would be a challenging position to moderate during B-R discussions.

**Participant 27** had an interesting point where they stated that 'many studies have shown that patients tend to go for a higher risk than a scientific panel, so it is important the assessment committee is balanced, including patients, doctors, scientists and regulators.'

*The perceived benefits of incorporating patient views in B-R assessment*

Interestingly, a common theme that emerged from the patient advocacy group's statements about the perceived benefits of involving patients was around the acceptance of risk. **Participant 01** acknowledged that regulators will have a 'better understanding of the amount of risk patients are ready to take' by involving patients. Correspondingly, **Participant 06** stated that 'patients are the ones that can describe in a more accurate way the benefits and side effects of medicines.' This was supported by **Participant 08** who highlighted that 'being able to demonstrate and understand more accurately the benefits and value to a person or their family, perhaps where the value of treatment will have been over or under-anticipated by the researchers [...] is helpful.'



**Participant 14** stated that ‘patients can give valuable insights into the lived experience of disease/conditions. They bring more than just a ‘medical’ experience and have valuable insights. Also, in the UK, pharmaceutical companies can have very little/no contact with the patients that they are developing drugs/interventions for. I also think patients will value something more if they know that other patients have been meaningfully consulted. I think they will believe the views and experiences of other patients, with lived experiences, over the possibly-hypothetical views of researchers, developers and healthcare professionals.’

**Participant 24** also agreed with these concepts when they stated that ‘patients are the ones living with the disease and therefore the ones that know better what it means in practical terms, they know better than anyone else what they are willing to accept (risks) to have benefits in exchange. Having their voice heard will make them feel empowered to make better decisions even in other aspects of the management of their diseases.’

*The perceived risks / negatives of incorporating patient views in B-R assessment*

Participants also understood that there was a possibility that patients would be willing to accept too much risk if they are in need of a viable treatment. Thus, **Participant 01** stated ‘that patients want a cure so they can be not cautious enough and want things going on too fast.’ This was supported by **Participant 06** who divulged that ‘there is a possibility that patients could accept medicines with lower level of benefits due to the absence of alternatives.’

**Participant 07** touched upon the challenge of method and logistics in particular: ‘I imagine it will be difficult to include patients.’ Likewise, **Participant 13** fully appreciated the logistical issues when they stated that ‘views could be lengthy leaving the need to interpret responses.’ This is particularly apt when undertaking a PhD research study involving large volumes of qualitative interview and focus group transcripts.

The theme of 'adequate representation' was also evident. Hence, **Participant 08** noted that 'some patient views will be very personal and subjective - their experience may outweigh a perception of possible benefits to others from a treatment if theirs was inappropriately delivered and their experience was poor.' In addition to this, **Participant 10** brought to light issues related to 'emotional and political bias.'

**Participant 12** noted that there is a need to ensure sufficient patients are involved to avoid skewed results.' Interestingly, confidentiality was mentioned twice by two different participants (**Participant 14 and 24**), whereas it wasn't mentioned at all in Survey P-R. This indicates patients' concern about the sharing of information about themselves and of the possibility of needing to divulge sensitive information to other stakeholders during B-R discussions.

As a consequence, **Participant 14** stated that 'I imagine that there is a risk around confidentiality/sensitivity in new drug developments.' They also commented that 'while many individuals can well represent their own views and experiences, unless they have a lot of contact with others living with the same condition/disability they may not be able to represent a wider experience. This is a limitation' indicating an understanding of the adequate representation issue. They described how 'patient experiences can vary widely, so again this will only give you a 'snapshot' of possible insights. This is why involving patient representative groups/advocates/charities can be of benefit as they can often represent the views of many more people living with the condition/disease,' which is a good example of the patient's insight.

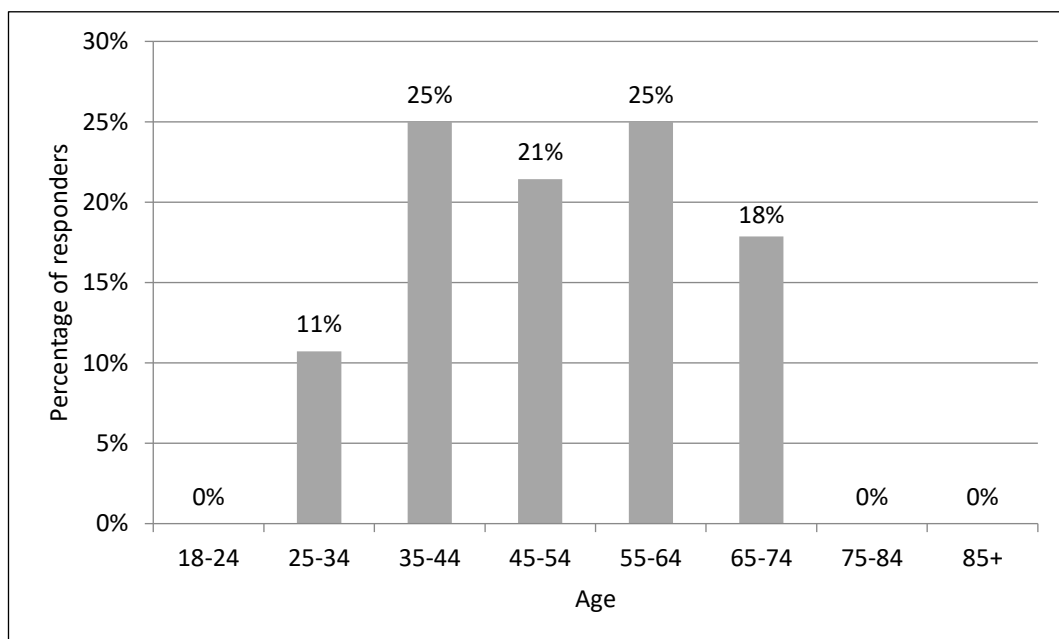
**Participant 15** also mentioned the identification of relevant patients as 'the patient must be someone who can assess the relevant population concerned. A one-person view could be very biased.' **Participant 20** also mentioned that it 'could be challenging to get target patient groups involved.'

**Participant 18** commented on finances, the only participant from Survey PAG to do so. They observed that there was ‘potential to make the drug more expensive as another layer is added to the development process.’

**Participant 25** noted that ‘sometimes, and especially for some patients with specific diseases (e.g., final stage cancers), their decisions might be influenced by the hope of living longer or with less pain. They might also not fully understand the benefits and risks and make a scientific assessment. This is why education and health literacy are paramount.’ **Participant 28** used the term ‘guinea-pig’ which was interesting. They did not wish ‘to be misused as a guinea-pig; to be involved in an experiment where you don't know the outcome; to take the risk, that the drug to be tested does not work or does impair your health or cause severe side effects; to replace a working treatment by a new drug with an unknown outcome.’ This does highlight the need for adequate training and education to assist the patient’s understanding of the process.

*Demographics characteristics of the participants*

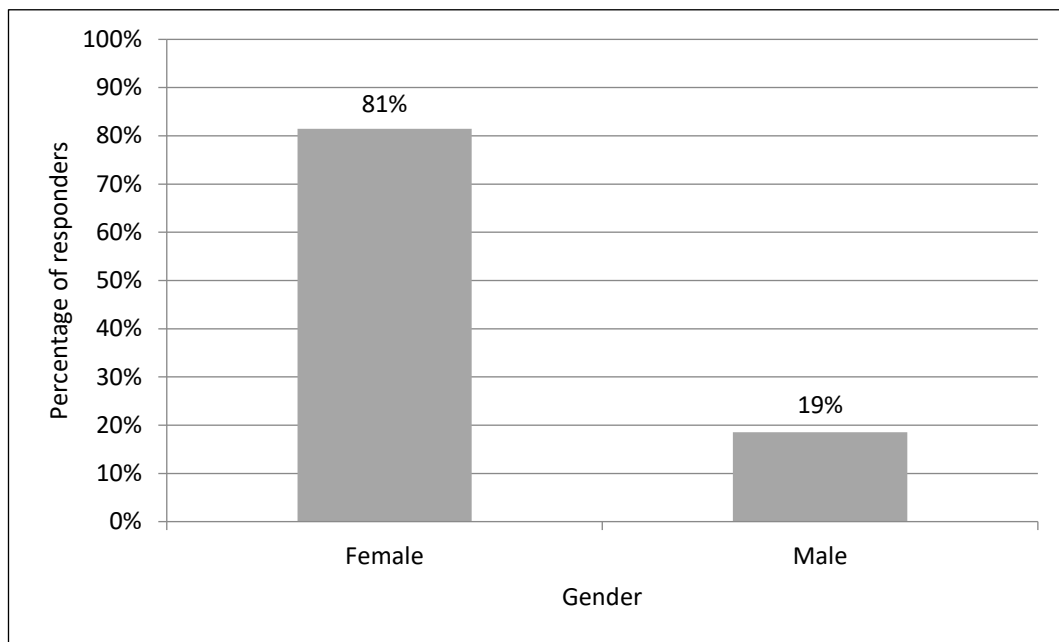
**Figure 4.15 - Age range of participants who completed Survey PAG**



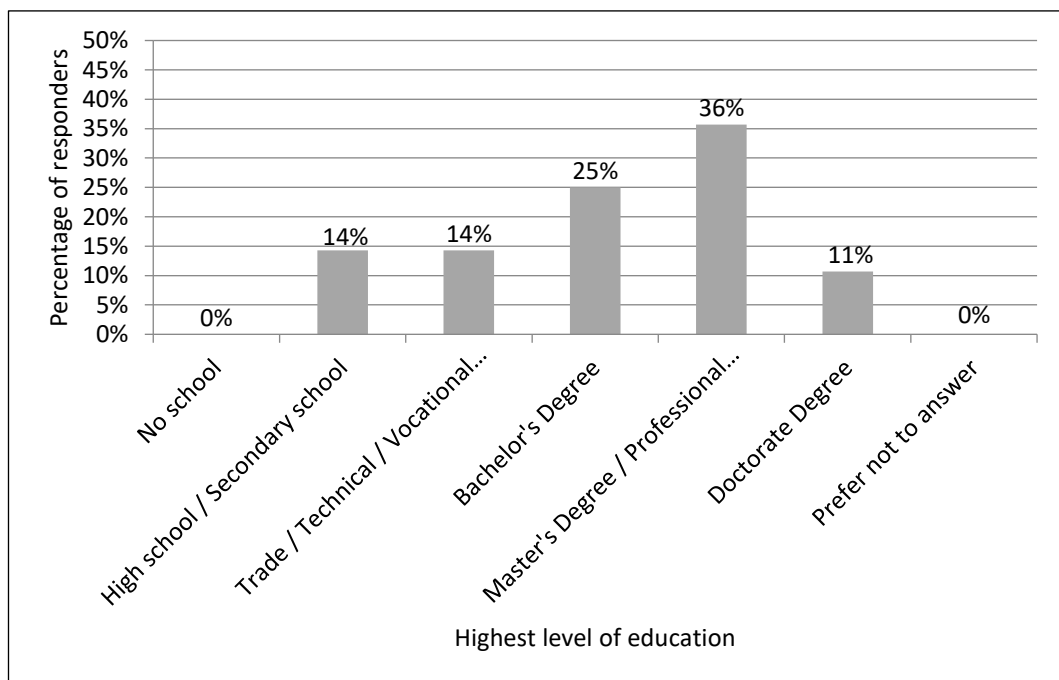
## Ethnicity of participants who completed Survey PAG

When asked to describe their ethnicity, all participants stated they were 'Caucasian' (n=25). Four participants chose not to answer.

**Figure 4.16 – Gender of participants who completed Survey PAG**



**Figure 4.17 – Highest level of education (Participants of Survey PAG)**



## Discussion

Phase I of the research presented in Chapter IV identified that patient involvement in B-R assessment was more widely implemented than the literature indicated. In addition, the awareness of patient advocacy groups on this topic was greater than originally anticipated, indicating recent initiatives had been successful in raising awareness. The objectives of phase I of the research study were to (1) survey pharmaceutical companies and regulatory agencies to discover the degree that patients were already included in benefit-risk assessment within their organisation, and (2) survey patient advocacy groups to discover their current knowledge on the topic of regulatory benefit-risk assessment of medicines. To achieve the overall aims, Chapter IV had four sub-objectives.

The first sub-objective was to identify the current involvement of patients in B-R assessment of regulatory agencies and pharmaceutical companies. The results confirmed that several stakeholders were in the process of developing initiatives to engage patients directly in their B-R assessment activities, in addition to the FDA and the EMA. Nonetheless, the organisations undertaking this type of work were in the minority. It should be noted that it cannot be assured that the data in Chapter VI covers all activities and initiatives across industry, due to the fact that many organisations did not respond to the survey. Thus, this was a limitation of this research element. Nevertheless, a range of organisations did participate including the European Medicines Agency and several large multinational pharmaceutical companies. The fact that 26% of organisations involved patient advocacy groups and 9% of organisations involved patients in their B-R activities, tends to the hypothesis that this was an untapped area for many organisations. Overall, the inclusion of patients in B-R assessment was seen as a positive development by the majority of participants. Generally, their involvement was advocated because of the benefits offered in providing an insight into the patient experience.

Whilst limited research had already been completed within this area, for example the project undertaken by Bernabe *et al.* (2014), it was decided in the current research plan to expand the types of organisations involved, not only focusing on European organisations but also involving several international stakeholders. Bernabe *et al.* (2014) reported how patient advocacy groups and patient representatives were involved at the EMA. However, there was no distinction between patient advocacy groups, charities or any examples of direct contact with patients. This was verified during the research, when direct telephone contact was made between the thesis author and the lead researcher of the study. It was confirmed that only patient advocacy groups who were existing members of the EMA's network were involved. It is understood that using pre-existing links and networks is essential for initial engagement, however, there was a risk of potential bias arising from pre-selection of this type. Participants emphasised how patient views were important, and, although patient advocacy groups were significant, there was a need to prevent them acting as a 'filter' to the patients' perspective.

When analysing the data, the job titles of participants who completed Survey PAG was of particular interest. Many of the participants had a range of roles and positions. Some were in fact patients, whereas others were senior staff within the patient advocacy organisation. This underscores the diverse nature of patient advocacy organisations and charities. By engaging with these organisations, it is not possible to be assured that the patient voice is always the one which is heard. This is largely because these organisations can be complex due to the variety of participants ranging from chief executives, directors, chairs, and committee members through to volunteers, patient representatives and patients.

The second sub-objective was to ascertain the challenges of involving patients in B-R assessment. A theme which emerged from the qualitative data was that of the patient's ability to remain objective. Participants from both Survey P-R and Survey PAG displayed this point. The fact that patient advocates also recognise this objectivity risk indicates their ability to understand the challenges involved, which further supports the case for their involvement. A number of participants identified the need for training and education, but this applies to all stakeholders. In addition, the logistics of involving patients was raised as an area needing further work. Another important theme was the underlying motivation behind the involvement of different stakeholders, including patient advocates. Thus, several participants described how individuals' can have ulterior motives, which may not always be patient-centric and may, in fact, be self-serving. Therefore, this is a risk factor that must be considered when identifying appropriate potential participants.

Participants were able to suggest a range of potential barriers to involving patients in B-R assessment, including a lack of established best-practice on how to do this, covering both the methodology of obtaining patient views and the structural and logistical challenges. They also commented that a lack of internal expertise in preference elicitation methods and application, better methods to capture patient input and creating a regulatory pathway to incorporate it. Patient representation was also a strong emerging theme, with regards to patient selection but also from an educational perspective. Health literacy was illuminated. When participants were surveyed about pinpointing possible solutions to the challenges of involving patients in B-R assessment (the third sub-objective), a range of solutions were suggested. The development of a standardised process was acknowledged above all, which also underscored the need to ensure any participating patients were as representative as possible. This indeed was a challenge which has still to be adequately addressed. Other solutions included the improved training of experts, training and broad representation and the inclusion of patients in licensing activities. Stronger, more active patient organisations was also considered an important factor.

The final sub-objective of Chapter IV was to recognise the current knowledge of patient advocacy groups concerning the subject of B-R assessment of medicines. The data outcomes were surprising in that the majority of participants, whatever their educational background and knowledge of B-R, all understood the principles and the concept well enough to comment. Almost all responses from Survey PAG showed at least some understanding of B-R assessment, without ever having discussed the topic previously. Therefore, with the right education and training, it is fair to concur that patients would be able to contribute effectively. Demographics were a topic which required further review and investigation. An important point regarding the previously published literature was that demographic characteristics were not described. This was true of the data obtained by Bernabe *et al.* (2014), so it was not possible to determine the diversity of the population who participated in the study.

In essence the research element presented within Chapter IV offers a unique contribution. It is argued that adequate patient involvement must consider the diversity of the population who are invited to participate. It should be noted that the work by Bernabe *et al.* (2014) was one of the first publications on the topic of patient involvement in B-R assessment, so it was leading the field at the time. Still, the addition of demographic information would have greatly enhanced that specific study. Phase I of the present research collected demographic information on all participants from both surveys. When reviewing these data, it can be seen that all participants from Survey P-R were Caucasian with a high level of education (the majority at Master's or Doctorate level). The participants who completed Survey PAG, however, had more varied educational backgrounds. This highlights the need for education and training, another emerging theme, yet it also demonstrates that a range of views are essential.



## Summary

- The fact that 26% of organisations involved patient advocacy groups and 9% of organisations involved patients in their B-R activities, supports the hypothesis that this was an untapped area for many organisations. Overall, the inclusion of patients in B-R assessment was seen as a positive development by the majority of participants. Generally, their involvement was supported because of the benefits it offered in providing to an insight into the patient experience.
- Participants were able to suggest a range of potential barriers to involving patients in B-R assessment, including a lack of established best-practice on how to do this, covering both the methodology of obtaining patient views and the structural and logistical challenges. They also commented that a lack of internal expertise in preference elicitation methods and application, better methods to capture patient input and creating a regulatory pathway to incorporate it.
- Solutions to increase patient involvement included improved training of experts, training and broad representation, development of a structured methodology and the inclusion of patients in licensing activities. Stronger, more active patient organisations were also considered an important step.
- Patient advocacy groups were relatively knowledgeable on the subject of B-R assessment of medicines. Therefore, with the right education and training, it is fair to concur that patients would be able to contribute effectively.

After analysing the qualitative data collected from Survey P-R and Survey PAG, and subsequent to the coding and thematic analysis using QRS\*NVIVO, several emerging candidate themes were identified. The candidate themes identified were:

- Adequate methods for involving patients in B-R assessment
- Adequate representation of patients
- Objectivity of patients
- Understanding and education
- Insight into the patient's experience
- Motivation and ulterior motives of stakeholders

At the end of both surveys, participants were offered the chance to continue to phase II of the research by participating in a semi-structured interview. The candidate themes were further investigated with these participants, and the findings are presented and discussed in Chapter V of this thesis.

**Chapter V: A thematic analysis of  
the current perspectives of  
regulatory agencies,  
pharmaceutical companies and  
patient advocacy groups on the  
involvement of patients in the  
benefit-risk assessment of  
medicines**

## **Introduction**

Chapter IV was integral to the overall aims of this research. It was imperative not only to understand the current level of involvement of patients in B-R assessment, but also the challenges that regulatory agencies and pharmaceutical companies had to encounter. This was essential if the aim of developing a framework for including patients in B-R assessment which would meet the expectations and requirements of all stakeholders was to be achieved. Phase I of the research presented in Chapter IV identified that patient involvement in B-R assessment was more widely implemented than the literature suggested. Challenges which were identified included a lack of a standardised method of including patients, as well as issues around ensuring the patients who were included remained objective and that they adequately represented others. Their motives were also considered, as was the risk that they may have ulterior motives, which may not be patient-centric and may, in fact, be self-serving.

The awareness of patient advocacy groups on this topic was greater than anticipated, as was their understanding on the concepts involved. To further develop the concepts and themes which were identified from the survey data, semi-structured interviews were completed with those participants who wished to take part in phase II of the research. The objective of phase II of the research study was (3) using qualitative semi-structured interviews, establish the opinions of representatives from pharmaceutical companies, regulatory agencies and patient advocacy groups, by undertaking thematic analysis of their views and opinions. In order to achieve this overall objective, several sub-objectives were established in phase II.

## **Sub-objectives**

- Discuss the challenges of involving patients in B-R assessment with stakeholders.
- Develop solutions to the challenges of involving patients in B-R assessment.
- Obtain rich data on the emerging themes from phase I of the research.
- Propose a framework for involving patients in B-R assessment and receive feedback from relevant stakeholders.

## **Methods**

### *Protocol development*

A research protocol was developed in line with good clinical practice and research governance requirements (Appendix V). Before the empirical component of this study element could commence, appropriate approvals were obtained.

### *Development of the semi-structured interview schedule*

A schedule of questions was prepared (Appendix VI). Questions were based around existing methods of including patients in B-R assessment as well as the challenges of involving patients and potential solutions to these challenges. The questions were divided into three topics:

- Topic 1: Benefit-risk methodology
- Topic 2: Patient identification and selection
- Topic 3: Possible barriers to involving patients

### *Cardiff University Ethics Application*

In addition to the surveys, the ethics application submitted to Cardiff School of Pharmacy and Pharmaceutical Sciences Ethics Committee also described phase II of the research and included the schedule to be used within the semi-structured interviews. The letter of approval is filed in Appendix VIII.

### *Recruitment*

At the end of both surveys used in research phase I, participants were offered the chance to continue to phase II by participating in a semi-structured interview. There is a consistent problem with obtaining key expert opinions due to the representativeness of sample populations (Christopoulos, 2009). There was a risk of positive selection for this research phase, conceivably because only those participants with an interest in patient involvement would move forward into phase II. However, this was a risk that had to be assessed and accepted. If a participant expressed interest in taking part in phase II, they provided their contact details within the survey. The researcher then contacted the participant directly and a mutually convenient date and time were arranged to undertake the interview, either at the participant's workplace or online, via *Skype*.

### *Semi-structured interviews*

Meeting individuals at their place of work was most interesting as it was possible to see the participant within their own environment. The participant signed a consent form on commencement of the interview, consenting to the fact that their interview would be recorded, transcribed and analysed. A standard schedule was followed for all interviews and they were recorded using an audio recorder. The interviews conducted over *Skype* were most challenging, particularly in the case of one participant who had an intermittent internet connection.

In any event, adequate recordings were obtained for all interviews. The candidate themes were further investigated with these participants and this information is presented and discussed in the current thesis chapter. Semi-structured interviews for participants from regulatory agencies and pharmaceutical companies were undertaken in London and Basel, Switzerland. Semi-structured interviews for patient advocacy groups were undertaken in London, Essex and also online using *Skype*.

#### *Recordings and transcription*

After data was collected via audio recordings and all interviews were complete, data was prepared for analysis. This was performed by the process of transcription. Transcription involved 'playing the recording in very short bursts' before 'typing up what you hear' (Braun and Clarke, 2013). At first, this seemed like a simple process, however, on commencing the transcription process it was quickly realised that this would become a lengthy and challenging process to undertake. The method utilised was that of 'orthographic' transcription, also known as 'verbatim' (Braun and Clarke, 2006). This style focussed on 'spoken words, other than sounds, in recorded data' (Braun and Clarke, 2013). It was noted that most qualitative research uses transcripts rather than coding directly from the audio recordings (however, some research does focus on audio or video recordings). Consequently, it was essential that the transcripts were of the highest standard possible.

A transcript of an audio recording 'is not a facsimile; it's a representation' (Braun and Clarke, 2013). So, in essence, it was expected that the transcript would not be an exact representation of the recording, it just needed to be as precise as possible. In order to ensure quality, 'a transcript needs to signal *what* is said and *who* is speaking' (Braun and Clarke, 2013). An orthographic transcript of high quality also 'needs to contain both actual words and non-semantic sounds, such as erm, er, and uhuh' (Braun and Clarke, 2013).

The primary reason for this is because changes to the way in which people speak can affect the meaning of what they actually said. Therefore, this method of transcription was adopted. Participants were given the opportunity to review their transcript and the emerging themes, to ensure the data was an adequate representation of their opinions. This process, known as ‘member checking’ is a form of quality control.

### *Coding of themes using QRS\*NVIVO*

The transcripts were uploaded to QRS\*NIVO and the qualitative data were coded and the data allocated to ‘nodes’: a method of analysis to assist in the generation and clarification of themes.

**Figure 5.1 - Screenshot of coding using QRS\*NIVO**

Name	Sources	References	Created By
Adequate representation	4	33	PIC
Methodology	4	27	PIC
Objectivity	4	20	PIC
Understanding	2	16	PIC
Patients are different to patient advocates	4	13	PIC
Patient acceptance	2	11	PIC
Motives	4	10	PIC
Education	2	9	PIC
Shared decision-making	2	8	PIC
Patient expert	2	8	PIC
Insight	3	7	PIC
Empowerment	3	6	PIC
Data driven	1	6	PIC
Equality versus inequality	1	5	PIC
Pharmacoeconomics	2	4	PIC
Personalities	2	4	PIC
Patient selection	1	4	PIC

### *Thematic analysis and generation of themes*

Thematic analysis, coding and the further validation of themes already identified was completed. After the transcription, it was important to read and to become familiar with the data, making note of items of potential interest. The next stage was to undertake coding, or organising the data into themes, before deciding upon which themes and sub-themes were prevalent across the dataset and which were of most importance. The themes identified were used to develop theory in phase III of the research study.



## **Results and thematic analysis**

Once the coding and analysis was complete, the data held on QRS\*NIVO was reviewed and compared against those data collected in phase I of the research. Several emerging candidate themes were identified during phase I, and these were verified and clarified during phase II. The candidate themes identified during phase I were as follows:

- Adequate representation of patients
- Adequate methods for involving patients in B-R assessment
- Objectivity of patients
- Understanding and education
- Insight into the patient's experience
- Motivation and ulterior motives of stakeholders

The data obtained during phase II verified these themes and the information collected during the semi-structured interviews added depth of meaning to them. The material collected in phase II was rich and aided the analysis of the research.

### *Participants*

Of the 23 participants who completed Survey P-R, 8 participants (35%) consented to be approached to participate in phase II of the study. In spite of this, after contact was made, only 4 participants moved forward into phase II (17%). Of the 29 participants who completed Survey PAG, 18 participants consented to be approached to participate in phase II (62%). Though, after contact was made, 8 participants (28%) moved forward into phase II.

Of the 12 participants whom participated in semi-structured interviews and completed phase II of the research, 1 participant (8%) represented a regulatory agency, 3 participants (25%) worked for pharmaceutical companies and 8 participants (67%) were patient representatives, patient advocates or worked for patient advocacy groups or charities.

The participants who participated in the semi-structured interviews are displayed in Table 5.1

**Table 5.1 - Participants, their role and association**

<b>Participant</b>	<b>Job title, role</b>	<b>Association</b>
SSI01	Pharmacovigilance expert	Regulatory agency
SSI02	Patient advocate	PAG
SSI03	Patient advocate	PAG
SSI04	Patient advocate	PAG
SSI05	Patient advocate	PAG
SSI06	Patient advocate	PAG
SSI07	Patient advocate	PAG
SSI08	Patient advocate	PAG
SSI09	Director of B-R	Pharmaceutical company
SSI10	Statistician	Pharmaceutical company
SSI11	Medical writer	Pharmaceutical company
SSI12	Patient advocate	PAG

*Thematic analysis and the clarification of emerging themes*

After analysis, the six candidate themes previously identified were confirmed and verified. Throughout the interviews, similar themes arose and also new information was identified. In addition to those candidate themes which were identified in research phase I, any new themes or concepts which emerged during phase II were also documented and investigated. The themes which were identified and verified during the semi-structured interviews are described in detail. In addition, a description of each theme will be presented along with examples of how the theme emerged from the data, by quoting participants with respect to what they said and how they said it. Themes which were most prevalent are described first and any sub-themes which were identified are also described.

*Theme I: Adequate representation of patients*

Theme I was prevalent across all interviews and consequently, it was the one which was most common. This theme was raised multiple times by all types of stakeholder, including participants from regulatory agencies, pharmaceutical companies and patient advocacy groups, indicating its importance to participants.

The first semi-structured interview was undertaken with **Participant SSI01**, a senior pharmacovigilance expert who was a member of several committees at the EMA. When asked about the involvement of patients within EMA committees, this participant was vocal about their experience of patient advocates within their organisation. The participant replied that 'at the level of our committee, you have only one representative of patient association, which do not represent all the patients [*sic*].' This statement was one of the first statements collected during phase II of the research, and it was not realised at the point of data collection, how profound this statement would be. It was a statement which would continue to emerge time after time within the dataset.

**Participant SSI01** described their experience of patient advocates. 'They have low (participation), because finally they really represent themselves, like I represent myself and you representative yourself.' In addition, 'they are a very old professional and probably too much old professional' [*sic*].

This was an interesting statement as was a valid point. All people do represent themselves, but a patient advocate should place others ahead of their own career and aspirations. The general feeling obtained from the discussion with **Participant SSI001** was that the patient advocate of which the participant was describing was only there in order to further their own agenda. **Participant SSI01** continued: 'So, you have one guy representing one type of illness, I don't remember who he's a representative for, but it's not very efficient to be honest [...] It's a big problem but my problem in your approach is that finally you will talk with patients which are more involved in a patient association.'

**Participant SSI01** also commented on how patients are selected: ‘now there is probably one main reason (for whom they select) is that most of the patient association (they use) have links with industry and so we probably choose only ones we know.’

**Participant SSI02** was a patient who represented other patients as part of a patient advocacy group and raised the importance of adequate representation. When discussing the involvement of patient advocates at the EMA level, **Participant SSI02** was quick to point out that they were ‘missing the key factor,’ referring to the lack of actual patients involved. **Participant SSI02** questioned how other patients are able to represent others if they have not experienced the condition themselves. The participant used their own experience to back up this query: ‘I suppose really I am only thinking about pain meds because that is the only thing I can really talk about.’ It therefore appeared as though this participant did not feel they could describe other conditions or treatments which they had not experienced.

**Participant SSI03** was a patient who represented a large national patient advocacy group. This participant had previous experience of advising panels at the National Institute of Health and Care Excellence (NICE) on the cost effectiveness of drugs. NICE have a role of not only assessing B-R but also pharmacoeconomics, so this participant’s views were particularly unique and this signified an interesting contribution to the data. **Participant SSI03** detailed that ‘we’re fortunate because we’ve got a big large patient supporter base who are very active, proactive, so when we did our survey we got hundreds and hundreds of patients because it’s a highly motivated patient group. But if you’ve got a rare condition where you might only have 30 people affected, what do you do? Bring all of them in? Sometimes they’re hard to reach.’ The participant was describing how, although they act as patient representatives, they have large networks of patients who they aim to involve as much as possible in all their initiatives.

On the subject of patient involvement within NICE however, **Participant SSI03** commented that ‘well, I think quite a lot of it is still tokenistic but it’s better than it used to be.’ Tokenism was a sub-theme which emerged often. **Participant SSI03** continued: ‘so, by the time they get to patient engagement, you know, it’s, “Oh well, we’d really like to involve as many as possible but ideally they should be no more than a mile away on the Underground,” type of thing. And then, “We’ll find somebody, we’ll find a budget to pay for the tea and coffee”.’ This was an interesting perspective as it highlighted how patients which are involved are those most easily accessed, for example, those who are local. This was similar to the system used by the EMA described by **Participant SSI01**. In addition, the level of involvement was deemed by **Participant SSI003** to be inadequate and tokenistic when they specified that ‘we were all excluded which I found very frustrating, because I had to sit silently as an observer and there were things where I felt if I had the opportunity to speak, with my long knowledge of dealing with thousands of patients over ten years, etc., that I could have had a voice there.’ The patient’s voice was an important sub-theme to Theme I.

**Participant SSI04** was a patient advocate from a national patient advocacy group. This participant was concerned that some patients may not be adequately included in initiatives such as this ‘either because they’re not well enough, because they don’t have the intellectual ability to be able to do it or because the actual fear of it is just too much. So, the challenges will be essentially trying to find a group of patients who are truly connected enough and able to do it.’ This was important because the method of selection will impact the overall views and opinions obtained. **Participant SSI004** said ‘then, of course, you are self-selecting out others.’ After being questioned on how represent other patients, **Participant SSI04** replied that ‘I will try very hard to give as many views as I can when I’m representing people. Other people can’t stand back and do that and again you’ve just go to assess what is said, knowing that that could be the problem but that is no different to any other group of people.’

**Participant SSI05**, a senior member of staff from a UK-wide cancer charity, raised concerns about how the size of a patient organisation affects their level of contribution. They stated that ‘not every patient group can carry at the same level of surveys or data collection as each other, which I think is a challenge.’ This is a good point, since better funded charities are more likely to have more resources, so they would have stronger patient engagement initiatives. Therefore, even patient advocacy groups at the organisational level are not comparable, due to their assortment of differences. When commenting about individual patient representatives, **Participant SSI05** highlighted that ‘when you have one or two patient representatives, while that depth of knowledge and personal experience is really valuable, there is no guarantee that that’s going to be representative of everyone’s views. **Participant SSI05** continued:

‘Just thinking about <<type of cancer>>, and this is I suppose just from experience of talking to people, it’s not backed up by research, but I think people’s different treatment experiences, have they been on prior treatments and their experiences of that will certainly influence what they think about a new drug, so the side effects and benefits presented by something new might appeal to different people depending on what their previous experience of being of a similar or different type of treatment. Age, I think will probably have a factor [...]. I think in terms of more demographic type backgrounds, I don’t know. I think that would be interesting to see if, for example, different ethnic backgrounds might have different views on benefit and risk of treatment but I think that is too difficult to say really.’

This was important, as **Participant SSI05** raised the possibility where differences in demographics could affect the opinions raised, by using age as an example. In addition, they also noted that potential differences could exist between different ethnic groups.

**Participant SSI06** was a patient from a much smaller charity compared to that of **Participant SSI05**. Like **Participant SSI05** though, they also had concerns about how different sized organisations would inevitably implement different levels of engagement, depending on their resources. **Participant SSI06** replied that ‘I think that is difficult, because the patients, generally, come from charities who have very little funding.’ Participant SSI06 described how funding for patient initiatives is always an issue.

‘Although the charity pays for the people to be there; for their travel, accommodation, etc., it takes time out from the other work that they’re doing for the charity, which obviously isn’t covered. So, that can be difficult, whether that person is actually a volunteer or a paid member of staff within that charity. There is a time element constraint for some charities in that, so I’m not sure how big the pool is that they can draw from for there to be more patients.’

**Participant SSI06** also had an opinion on patient representatives’ understanding the patient’s perspective. They argued that training and education are required not only with patient advocates, but also with patients themselves, when they described that:

‘I know how much pain I’m in. I know how tired I am. You can’t measure it. So, if I tell you it’s a ten today...I can’t get out of bed, I hurt so much. You know? So, yeah, patients need advocacy training to be full partners and you have to accept that some are capable of that and others aren’t.’

**Participant SSI07** also represented a small patient advocacy group. They also understood the challenges of ensuring adequate patient representation, when they replied ‘I think it’s the challenge of getting patients who are representative which I think can be tricky.’

**Participant SSI07** also noted that it would be important to engage patients from a variety of backgrounds when they replied that patients should come from 'a variety of ages, because younger people may have different ideas on which side effects are more or less helpful than older people because they prioritise different things in determining their quality of life.'

Another patient advocate, **Participant SSI08**, also had concerns about individual patients acting on behalf of the larger patient community. They described patient representation as:

'Having a say in all of the parts of the processes that are relevant to your community. I mean, I know you can have one patient trying to represent patients generally but I think that's not really good enough. It has to be a patient with the disease at the meeting about that disease. It can't be generic and I know sometimes it's impossible to have a representative for every disease at every meeting, obviously, but for the important things like a risk-benefit for a medicine for a particular disease the person should be definitely someone with the disease.'

**Participant SSI09** had a different and unique perspective compared to previous participants, as the Director of Benefit-Risk Assessment at a large multinational pharmaceutical company. **Participant SSI09** confirmed that 'my difficulty is to find representative groups, or a large organised patients' organisation, you have a very different kind of people talking to you.' **Participant SSI09** was in the process of developing a patient engagement initiative within their organisation and had therefore identified several challenges unique to them. They were taking an international perspective, which was part of their responsibility. **Participant SSI09** asked 'how would it be for the patients you see in Guy's Hospital compared to people I would treat in Nigeria?' This is a valid point and demonstrates the complexity of this topic when considered at the international level.



**Participant SSI09** continued ‘if we really will do this properly, that’s what we will have to consider. So, the benefit-risk that’s acceptable for EMA might be very different than what the South African’s health authorities will accept there.’ As a pharmaceutical company working across multiple countries with differing regulatory requirements, their approach to patient involvement will have additional considerations. On the topic of if patient advocacy groups represent patients, **Participant SSI09** replied:

‘I have patients’ organisations, patients’ advocates, I have field knowledge ... and this is one thing drug companies do well. So, usually we’ve established a network where we can get data, but this is I think the weak link in all of this: how we standardise or...yeah, standardise would be the best term, but not ideal, patient identification. So that it’s meaningful. Because you’ll get the opinion that you choose to get, and the bias you choose to give, and that’s dangerous. Well, it’s dangerous if you don’t recognise it.

This was an important comment regarding bias, which emerged as a theme in several interviews. **Participant SSI09** continued, ‘if you recognise the bias, you can measure it, and can (for lack of a better word) neutralise it. It’s a...I mean, bias, we have this everywhere. We filter, that’s the thing, but how do you filter this? I’m not sure that we have necessarily the right method so far or recognise it every time. So, that’s why, if you want my own preference, wherever I could I’d like to use broad multi-national selections of patients.’

**Participant SSI10** also had a unique perspective, as s/he was a statistician involved in B-R methodology. This individual was an industry expert in developing quantitative methodology and was also a partner in the IMI-PROTECT collaboration. Hence, as a quantitative expert, their views were indispensable.

On the topic of patient identification and selection, **Participant SSI10** described how previous initiatives had weaknesses: 'generally, focus groups think diversity is good. Is that too diverse, you know, are you mixing apples and oranges, so to speak? Or could they dominate a conversation? Yes, and also the sort of person who, you know that you're able to travel to a focus group and take part in it, it shows that you're not, you know, the sickest of patients.'

**Participant SSI10** also compared how patient involvement initiatives are often not like the 'real world' by comparing them to clinical trials. This participant presented the idea that those patients are not eligible for clinical trials may in fact be the patients who would provide the most important insights with regards to their condition. **Participant SSI10** stated that 'in clinical trials, the patients are often generally healthy, except that they just have one problem, you know. If they had multiple co-morbidities they may not be eligible for study, but maybe that's the sort of person who you want to get values from. At some point, maybe this is done post marketing, you know, but at some point.'

**Participant SSI11** was a medical writer within a pharmaceutical company responsible for producing medical reports and summaries, which would later be used within the context of B-R discussions. **Participant SSI11** was keen to explore methods of enhancing their reports by including the patient's perspective, however they also highlighted the challenges of ensuring adequate representation: 'maybe for economic reasons, for disease reasons or age reasons. The youngest people are hard to get their opinions articulated.'

The last participant to take part in study phase II was **Participant SSI12**, a relatively inexperienced patient advocate who had recently commenced work for a charity. Considering their limited experience, they had important insights about adequate representation.

**Participant SSI12** predicted that ‘it won’t be easy to engage with a patient ‘s representatives because, a, it’s getting a mix of people that represent, I find that in relation to anything that I’m involved in, it’s usually the people that squeal the loudest that get included.’ The latter statement was particularly interesting as it highlights another emerging theme of ‘strong personalities.’ This theme was not just applicable to patients, but to all stakeholders and it is an important consideration. **Participant SSI12** also commented on the appropriateness of some patient advocates:

‘They’re not necessarily always the best people that you need most of all and you also probably need a mixture of understanding about the process too I would think because sometimes somebody who is totally in the dark can come up with something that is fairly simple and should have been thought of already. So, I think it’s getting a mix of people and it’s probably also, it’s a difficult one, a lot of people that are involved with medicines seem to be also sick themselves.’

**Participant SSI12** described examples where they noticed certain individuals had a loud voice which affected the dynamics of the group. This is an important point as this is relevant to focus group methodology; where participants may not feel able to speak up due to the actions of another. They stated that ‘they were arrogant and you wanted to sort of say, excuse me, how do you represent? I just think that that’s totally wrong.’ **Participant SSI12** continued: ‘It just bothered me that certain people were representing, as you say, I presumed, the entire patient population’ and ‘I think whenever you start getting arrogant or you know blasé about the whole thing I think then it’s time to move on.’ This was particularly apt and supported the comments of **Participant SSI01** regarding patient advocates at the EMA level. Some individuals were perhaps no longer adequately representing patients and this must be addressed. These data were further investigated by the emerging sub-theme of ‘patient advocates are not the same as patients.’

*Sub-theme – Patient advocates are not the same as patients*

This was an emerging theme which on analysis fitted most appropriately as a sub-theme to the Theme I (Adequate representation of patients). **Participant SSI01** was the first to make a comment on the role of the patient advocate within EMA committees which the participant resides over. **Participant SSI01** stated that ‘at the level of our committee, you have only one representative of a patient association, which also do not represent all the patients.’ This impacted on patient selection as ‘already bias was introduced by selection’ (**Participant SSI01**).

**Participant SSI02** commented on the staffing of patient advocacy groups, for example that other types of engagement occurred without direct patient involvement. They stated that ‘to be a patient advocate, you have to be the first part of those two words. You have to be a patient.’ **Participant SSI02** continued ‘you can’t possibly be a patient advocate unless, at the very least, you have lived with someone that is ill. It is a whole different ballgame.’

**Participant SSI03** described the concept of the ‘expert patient’ which they, as a patient with the relevant condition their advocacy addresses, had strong feelings about who was appropriate to act on behalf of other patients. **Participant SSI03** said ‘where you’ve got professional advocates, they may not have direct experience of the condition, but they’ve got experience of advocacy and policy and they can speak the language, and they’d be usually very good at summarising information and presenting it in a clear way, which is a benefit.’ This was a positive example of how expert patients also offer a unique and important contribution.

**Participant SSI04** had a different viewpoint. When comparing patient advocates and patients, **Participant SSI04** stated that ‘they have a very useful point to be made, but it’s very interesting, I’ve worked with patient representatives on some boards and they simply don’t get it.’

**Participant SSI05** approached the comparison of patient advocates and patients from a philosophical perspective.

‘This is very philosophical, but I think they’re not the same because in a sense we represent patients but we’re not a patient, so there is certainly that separation, and I think if we are going to gather patient views it’s got to be more than having one representative. That representative has to be accountable to all those patients, as far as possible, which is why it is so important to get together as many robust views as possible and to reduce that uncertainty, because I think if you just nominate a patient representative without that patient representative having the feelers out and being able to gather that information, then you’re not really doing patients any service and there is a risk with patient representation that has to be done very carefully to make sure it’s democratic.’

This demonstrated that **Participant SSI05** was aware of the limitations of their role as a patient advocate but addressed them with a transparent approach. Although examples of inadequate patient advocacy were prevalent in the dataset, this participant demonstrated that on the other hand, patient advocates also make a vital contribution. Correspondingly, it all depends on the individual, their motives and their awareness of their own limitations and impact. **Participant SSI005** continued:

‘Patient advocates can represent the views of others. The patients become very informed, not just about their own condition or about how it affects them, but they do become informed about the condition generally. So, I think they can certainly represent the wider experiences of others. [...] They look at the data. They look at evidence. They speak to people and they do try very hard to represent the widest possible views and experiences. I think if we can support them to do that better and more robustly, then that’s a positive thing.’

**Participant SSI06** highlighted how a certain type of individual would become a patient advocate and therefore, by default, does not represent all patients, by citing the EMA as an example. They presented the argument that ‘you know, you’re not going to get a shrinking violet saying, “Yeah, I’ll represent us on the European stage *[laughing]*.’

**Participant SSI07** also commented on the ability of some individuals to represent others, when they said ‘they can’t represent, not unless they’ve actually experienced the disorder. I think patient advocates vary. There’s no one generic type. But, I think the core information comes from patients who experience the condition and who are taking medication for it.’

**Participant SSI08** had a similar stance to the previous participant and described how patient advocates are so variable in their suitability and approach. **Participant SSI08** confirmed in addition that, within their organisation, patient advocates ‘usually are patients, but sometimes they’re not.’ They continued:

‘I think a patient advocate should really be a patient, it’s probably advantageous but I think they need to be one with a sensible head on and they need to leave the emotion at the door because I just think they could do a lot of damage to your patient group. Because I know that there is an impression that some people think “Oh my God hysterical patient, like, is that what we’re gonna get?” And you don’t want to ruin your chances of being taken seriously and being credible if you turn up distressed and wailing and too emotional. I’m not trying to say that these things aren’t important and serious but I think the best thing you can do is have a patient rep or advocate that has got the insight of being a patient but can stand back from the minutia of having the disease.’

The comments about emotion and the term ‘hysterical patient’ were interesting and highlighted this patient’s concern that their views were not seen as objective.

**Participant SSI09** had the perspective from industry and they too understood that patient advocates were not the same as patients, though, their input was paramount. Accordingly, **Participant SSI09** replied that ‘I have patients’ organisations, patients’ advocates ... and this is one thing drug companies do well. So, usually we’ve established a network where we can get data but this is I think the weak link in all of this: how we standardise or...yeah, standardise would be the best term but not ideal, patient identification so that it’s meaningful. Because, you’ll get the opinion that you choose to get and the bias you choose to give, and that’s dangerous. Well, it’s dangerous if you don’t recognise it.’ Again, like **Participant SSI05**, this participant recognised the limitations of their approach, while continuing to develop their initiative with as much transparency as possible. **Participant SSI009** recognised that patient advocates were ‘a necessary surrogate in many situations. We need to recognise, like any surrogate, they’re not ideal [...] As long as we don’t make it what it isn’t. But we use them (patient advocates) because there’s nothing else you can do.’

**Participant SSI10** offered a different perspective. Although this participant recognised patient advocates were different, they argued that ‘they’re pretty close. Because, often, they are patients. They may not be the typical patients, because of the nature of wanting to be an advocate. They probably have a good idea of the kind of scope of what patients think in general. And they’d be very informed in terms of, you know, the disease and the literature and anything like that.’

**Participant SSI11** also mentioned the patient advocate as being a certain ‘type’ of individual. They mused that ‘the advocacy groups are composed of patients who are eager to have their opinions asserted, whereas we’re missing the ones who don’t want their opinions asserted and so we don’t have access to what those opinions are as much.’ **Participant SSI11** also noted that ‘we need to recognise that there are certain self-selecting patient advocates who will get involved early, because a lot of patients don’t want to bother with the details of these definitions.’

*Theme II: Adequate methods for involving patients in B-R assessment*

Topic 1 of the semi-structured interviews were centred around the methods of involving patients in B-R analysis. Participants were directly questioned on this topic, which meant it was inevitable to emerge during the interview. Be that as it may, it was surprising how often methodology was mentioned throughout the interviews, even when it was not the direct topic of conversation. Participants recognised the difficulty not only in identifying and selecting the right patients to be involved, but they also had concerns about the methods utilised to include them.

**Participant SSI01** was interested in using both quantitative and qualitative approaches. During interview, there was a robust discussion about a semi-quantitative concept, where patient preference elicitation could be used in combination with qualitative focus groups. **Participant SSI01** confirmed that this approach ‘explores two different ways, but it’s not possibly for the same goal. It’s for two different goals, so, the two approaches are very interesting for me.’

**Participant SSI02** found the idea of qualitative focus groups appealing. They confirmed ‘that would be very interesting, because it would be good to have a discussion with someone that was thinking about going on a drug I’ve taken and they hadn’t been on yet.’ **Participant SSI02** understood the need to review information in advance of any such focus group. They noted that ‘graphs, pie charts and anything else visual are always easier (to absorb).’ **Participant SSI07** also described how they would like to review B-R information if they were invited to do so. They would like to see ‘a mixture of data: bullet points and bar charts, pie charts. Make it brighter, make it bold, and make it attractive, yes. And also include links to where they can find out more information.’



**Participant SSI03** commented on how as a patient representative for NICE committee meetings, they were provided with lengthy dossiers in advance of their committee meetings. They pointed out however that, due to its length, they 'didn't think the NICE Committee had had enough time to read the dossier.' **Participant SSI03** described the dossiers and how published articles were provided with commentaries: 'The commentaries are not always positive of course [...]. Some intermediary will take the information and usually, with the help of one of our medical experts, we will write up, what I like to think, is a lay-friendly version.' **Participant SSI03** also described how they were aware of quantitative methodologies, also employed within their NICE committee meetings. They stated that they use ranking to rate benefits and risks: 'they'd gone through a process of pre-ranking through quantitative work to try and avoid that small (sample) size issue.' **Participant SSI03** commented how, in addition to patients, they thought other stakeholders were essential to be included. **Participant SSI003** emphasised the importance of other stakeholders: 'pharmacists, because we know adherence is a huge issue, and nurses, you know, are increasingly involved in prescribing and specialist care' (**Participant SSI03**).

**Participant SSI05** described the challenges of implementing a valid method of involving patients in B-R.

'The challenge is also around getting real world data from patients who haven't actually had any experience, so that's the conundrum of benefit-risk. So, we do regular surveys, interviews with people, but again it's a small number of people or we try and bring in supplemented data from other studies, if there is a particular side effect associated with a drug we've got evidence, people's tolerance for that side effect, we can bring that in but it's not... we're aware that it's limited.'

**Participant SSI08** understood the logistical challenges of patient selection and identification, and how this influenced the development of an adequate methodology: 'I can see the administrative nightmare of pulling a patient from the correct disease group into the meeting about that disease because they might not have a patient directory for each or they might not have somewhere they can access that patient. But, I think they should at least try' (**Participant SSI08**).

As **Participant SSI09** was developing methodology to include patients in B-R discussions, they had an important insight and they also appraised the proposed framework which would be developed from this research study. Participant SSI09 argued that this was a considerable task for the organisation. They commented that they were collaborating with the IMI-PROTECT consortium in order to standardise their approach: 'We're trying to see which methods we would use. We're doing this with now I think it's about eight or ten companies who have joined. Academia are very interested so they're part of the process. On further discussion, **Participant SSI09** confirmed that 'by preference I'm a quantitative person, so we said let's move to quantitative methods. Semi-quantitative structured benefit-risk is not exactly quantum physics yet, but we're working toward developing these methods.'

When proposing a semi-quantitative framework involving patient preference elicitation and focus groups, **Participant SSI009** stated 'the challenge of this is it takes a lot of effort to validate, like to really know you got the right choices (B-R criteria) and that people have actually understood what these choices were and expressed it in a proper way.'

This is an important challenge, and one that can only be addressed in collaboration with all stakeholders. It was not possible to develop elicitation methods during research phase II, as the complexity of an individual drug's benefit and risk criteria are lengthy and require various technical input.

**Participant SSI09** confirmed that ‘I would like to end up in a truly quantitative approach, but when you get into this you realise there’s nothing: nothing validated and no clear way to get there, so you fall back to the semi-quantitative approach.’ When discussing qualitative focus groups, **Participant SSI09** confirmed that ‘focus groups are not something that just got invented. There’s a science to this. It’s not the most rigorous, I mean we’re not talking gene splicing here, but that being said we need to use what’s there, try to keep improving this, because I do find that it’s your input that will determine your output, and if your input is incorrect or incomplete then you suffer a risk.’

This is an important point. **Participant SSI009** was referring to the quality of the focus group itself. By asking particular questions, the focus group is led, much like the discussion was for the semi-structured interviews. Therefore, there is a risk that the moderator of the focus group can in fact introduce their own bias into the data that is collected. The thesis author had to take this consideration into account when developing their own B-R framework. **Participant SSI009** concluded that although challenges remained, new methods of patient inclusion would be a valid contribution, when they stated that ‘I think people have to get beyond this and that, in a sense, this will come, this will get better, more structured, and will be applied by different players in the healthcare system.’

As a statistician, **Participant SSI10** had an important perspective about the methodology of including patients in B-R discussions. Firstly, the participant described their background in greater detail:

‘A bit of history, actually my background is in statistics, or my formal training's in statistics and then I moved into health economics and the health economists are very advanced in eliciting not just patient preferences, but, eliciting preferences in general. And then I moved into decision analysis, which is a way of kind of structuring and analysing decisions. And part of that discipline is you make decisions in a way to kind of optimise utility, so there are ways of placing values on outcomes

for the decision-making. So, there's a rich history in eliciting preferences.'

When presenting a semi-quantitative approach, which would involve patient elicitation and qualitative focus groups, **Participant SSI10** confirmed that 'a combination of these methods is mathematically robust, they all satisfy utility axioms and things like this. I think the real problem is the behavioural science aspect and how to codify and capture patient's beliefs accurately.'

**Participant SSI10** also commented on how data is presented during B-R discussions when he stated that 'historically, the benefit-risk assessment was a narrative. It's just a text description of the benefits and risks and it always says so therefore the benefits outweigh the risks.' **Participant SSI10** was pleased with recent developments to involve patients when they stated 'so, this is trying to make that process a bit more transparent.' When discussing the idea of a list of benefits and risks which could be presented to patients, **Participant SSI10** had the following comments:

'Well, you can be completely surprised by what comes up from what actually patients are most concerned about in diseases, it might not be what you first thought, not experiencing that disease. But at the same time, if you look at the list of risks that you see in a clinical study, it's hundreds of risks, say 4, 500, risks and it would be overwhelming. So, it's a very difficult question to answer. I mean I sympathise that there should be an open part of this, it shouldn't be constrained by a list, but maybe it needs some structure, I don't think you can be completely free and I think having lists can help prompt someone to... so I think some hybrid, I don't know if that's the sort of.'

When discussing focus group methodology, **Participant SSI10** confirmed 'I don't have a clear opinion on that. In fact, it would be interesting to see if it makes a difference, you know, between a smaller group and doing things in a focus group, an interactive focus group and kind of a large independent sample.'

**Participant SSI10** also commented on patient representation: 'To me, it's fundamental that the patients should be representative of the target question, the research question. You find a research question and in that is a target population. And, ideally, there should be real world evidence, not the kind of selective patients you know in a study.' When discussing the idea about presenting patients with hypothetical scenarios, **Participant SSI10** noted some key issues with this approach:

There are, perhaps, extra complications in that asking a patient about adverse events before they've taken the drug and haven't experienced them, and asking their opinions about them at the end of the a study where they may have experienced an adverse event could change their opinion on it It's very different, to you know, imagine what constant nausea feels like and then actually experiencing constant nausea, it's better or maybe it's worse than a figure of experience. Or patients who've had the disease for a long time and have somehow adapted or coped, developed coping mechanisms compared to someone who's brand new.'

**Participant SSI11** also noted issues with presenting data to participants in advance of a focus group or when they stated that 'maybe it will be the order that you put the benefits and the risks when you're asking them about them, they influence them when they're doing their ranking.'

### *Theme III: Objectivity of patients*

The objectivity of patients involved in B-R discussions was a theme which arose numerous times during phase I in particular. Yet, although participants were quick to highlight a patient's objectivity, a number of participants in phase II gave examples, either, where their objectivity was questioned or where they had seen examples of a lack of objectivity of others.

**Participant SSI01** responded that they use 'gut feeling' during their B-R assessment meetings. When making their decision, they argued that, 'for example, if I take the example of, say, liver injury or skin injury, I am the only expert able to give *my* opinion but its only *my* opinion and what I try to say to the regulator is that they should use very useful method like algorism to assess the causality between an event and a drug. They don't use it, so I said 'believe me.'

As a patient representative, **Participant SSI02** was well aware of the need to remove emotion from any discussions, 'yet, I suppose, if you are desperate. I suppose there is always going to be bias in things.'

**Participant SSI03** had seen evidence of bias in NICE committee meetings, and not from patients, but 'bias from people dominating meetings who've got a particular viewpoint. When discussing the potential bias of patients, **Participant SSI03** compared it with the inherent bias that all people present:

'Well, there's a huge bias, isn't there? It's either tokenistic or it's usually biased, especially for a patient organisation because the majority of us are assisted in some way by pharmaceutical sponsorship, even if it's not the sponsoring company. And you try your best to be completely agnostic but clearly if there's a drug which appears to have worked in a trial you'd be mad not to support it. But you have to be extremely careful about being seen to be or being biased in favour of the drug. And the data is hard to interpret. You don't see all the data of course; you only see what's published. You instinctively look for the positives in

data, particularly if it's been a well-regarded trial. And again, when you start to look at the dynamics of the people around and the voices, again, you could feel in that committee meeting I had somebody with perhaps a bit more knowledge or a particular bias could change the outcome of those decisions.'

**Participant SSI04** also commented on other stakeholders, 'I mean if you have a room full of doctors who are discussing a topic, they'll be biased.'

**Participant SSI05** understood why a framework was therefore necessary to reduce the likelihood of bias, 'I suppose that's why it's important to have some kind of framework rather than a survey which could be challenged potentially or a focus group run by a drug company and they happened to get results to say they preferred this type of drug.' **Participant SSI06** also noted that 'I mean, the pharmaceutical companies have got a wealth of bias.'

**Participant SSI07** was quick to point out that 'whenever you've got human beings you've got bias. Yes, in an ideal world everyone would go into a room and they would be very objective about their experience and their clinical findings, that doesn't happen [...]. It's very hard to get rid of bias, but you can reduce it by making sure it's a calm, you know, measured meeting. And everyone is given enough time to speak. And what you say is not going to be discounted in any way because you are not a qualified clinician.'

**Participant SSI08** had seen previous evidence of lack of the patient's objectivity, and examples of too much emotion. They thought that:

'In my experience of patients, bless them, and I am one of them, I mean it's an emotional subject, there is I think sometimes a problem with people being able to be objective about processes and outcomes. Separating it from their personal experience and their daily quality of life because when people are very sick, (A), they're probably not going to be involved in these processes because they can't be dealing with it

but (B), I just think that is one of the difficulties you get somebody who is very passionate but, like, overly emotional. In a way, you need to find someone who's a patient but who is objective.'

From an industry perspective, **Participant SSI09** was well aware of this challenge. Though, they had some recommendations on how to deal with this issue. **Participant SSI09** stated that 'I would like to think we can do this scientifically; we can come with arguments that everybody will agree to, say that that's the right methodology, these were the right samples, these are the right knowledge, and therefore your benefit-risk here differs from here, and while it might not be acceptable in that setting, or it might be acceptable in this setting, it may or may not be in another setting. But, remove emotion out of this.'

**Participant SSI009** described how one option would be to move away from the current system of using patient advocacy groups linked to the organisation when they stated that 'I think a big part of what we're going to have to do is step away from these very selected or bias groups. I don't want to say bias in a bad way, but to learn to work with probably the organised regional care unit, whether they're regional hospitals or primary care practices, to better understand most of these patients [...] And as much as we can, and that's not easy, and I don't say this in a pejorative manner, but avoid professional patients' groups, because it becomes a different thing. They don't think of themselves anymore, they speak for others, and what I want is the input of people as it affects them as a person; not how they think it affects the millions of other patients with the same disease.'

Even though the focus was on involving new patients, discussions were very much focussed around the objectivity of those stakeholders already involved. This was interesting and supported the general hypothesis that involving patient advocacy groups alone was insufficient, and processes must be developed which link directly with patients themselves.



Patient advocates are an important stakeholder, yet, they should contribute in collaboration with patients and not be used as an alternative.

*Theme IV: Understanding and education*

Another theme which emerged during research phase I and was verified during phase II was that of a patient's understanding and education.

**Participant SSI02** gave an opinion on who was best placed to make decisions. This was perhaps an example of the risk that patients could potentially 'over step the mark.' The thesis author does not support this position. It is vital patients are involved, yet clinicians and regulatory assessors are undoubtedly the most qualified to make licensing decisions. **Participant SSI02** stated that 'I think only we can assess the risk and the pros and cons. And I think as well you have to be... I am not talking just about aspirin or whatever, if you are talking about specific drugs for long-term illnesses.'

**Participant SSI03** highlighted that even as a member of a NICE committee, they sometimes struggled to understand. They said 'Because the language is completely alien, the utility of death or the disutility of death. I've no idea what they're talking about here half the time.' This participant was well educated, experienced in B-R discussions and they had made contributions at NICE committee meetings previously. Therefore, this acts as evidence that even experienced patient advocates need additional support and training. There is also a clear need for educating all patients, if they are to successfully contribute to B-R discussions. **Participant SSI06** also noted that the process is worthless 'if you don't educate the patient to take part properly in the background and within the whole process.'

**Participant SSI07** had a different point of view when they stated that: 'It's never a good idea to assume that patients won't understand simply because they do not have the clinical expertise. Patients are very, very good at finding things out themselves and asking questions as well. So, I think the best way to involve patients is include them, wherever possible, and then you learn where

best they can help.’ This was a valid point and one which is supported by the thesis author.

**Participant SSI09** also pointed out that ‘regulators ultimately serve patients, [...] their mandate is to help patients. I’m not sure they understand what it means fully; I don’t think they understand how profoundly it (involving patients) will change the way they will oversee and approve treatments and drugs. And, similarly for patients: I think patients think, ‘all of a sudden I’m going to be better cared for because I have input.’ **Participant SSI09** ended with ‘we need to not present this in a fallible way.’ Indicating the way in which training is undertaken will impact on the outcome.

**Participant SSI11** expressed concerns about the patient’s understanding of clinical documentation when they stated that ‘patients will have a harder time breaking down the entire portfolio, compared to if they’re led through it first. Ranking (of benefits and risks) would be good. It would also be of high interest to the industry people, in my opinion, because I can see that this patient group ranks this risk high or low.’ Therefore, a collaborative approach between regulatory assessor and the patients would be appealing to industry.

#### *Theme V: Insight into the patient’s experience*

When participants were questioned about the benefits of involving patients in B-R discussions, a theme which arose time and time again was regarding the ‘insight into the patient’s experience.’

**Participant SSI02** had a strong opinion on the matter when they stated that ‘nothing annoys me more when somebody says, “Oh I know how you feel.” I feel like saying, “Just don’t say that. Don’t say that to me because you don’t, you can’t.”’

**Participant SSI03** described how in preparation for NICE committee meetings, they would review relevant articles. They went on to say ‘so, there’s this one pivotal trial, in our case. I was just reading the Cochrane review of it

all. They don't seem to impress anybody. And also, they're only looking at a certain set of outcomes anyway; they don't seem to be looking at all the outcomes that are important to the patients.' **Participant SSI03** understood the importance of viewing data at the population level, yet also the relevance of the individual perspective, 'yes, there's the population level, but nonetheless, the patient's experiences can still bring a richness to the data which you don't see. But I would say on the main, they bring the richness to the data. It's not captured usually in the primary outcomes or the endpoints of clinical trials.'

When describing insight into the patient's experience, **Participant SSI04** highlighted that:

'I think we actually do look at things from a different angle. Now, when you're talking about patients you are of course talking about everybody, because basically, everybody is a patient. So, I would be talking about people who are long-term patients because it's mostly long-term patients who are well involved with their care, a lot of them have to actually juggle a lot of medications anyway. So, when we're talking about long term patients being in a cost risk-benefit analysis, I think that's absolutely essential, because they'll be looking at it from a completely different point of view from professionals.'

**Participant SSI05**, whom was not a patient but who acted on behalf of patients, also understood the unique insights which patients offer, when they stated that:

'I think we want to see better patient input at both stages. Also, to make sure that actually what goes into the system, so the right drugs are developed, and that we understand their value much earlier on. So, it doesn't come to the licensing or HTA stage and you find that it's actually only going to benefit a very small number of patients and we don't have the data to express that. It's trying to understand that much earlier on

in the clinical development process, that the right things come through the system.'

**Participant SSI06** disclosed that 'however empathetic you are, you can't really know what it's like. The patient is the only person that really knows what it feels like to have the condition and the only one that knows what the medication effects feel like.'

**Participant SSI07** described 'lived experience' when discussing the insights which patients offer. They argued that 'patients have the lived experience, they know what is meaningful in terms of benefits and risks because they live it. Also, patients often have done a lot of research online because so much is accessible and so they very often have a technically informed view as well as an experiential informed view. So, they are very good at telling you how it is and making points which perhaps someone who hasn't experienced the disease wouldn't think of. So, yes, they can provide invaluable input.'

**Participant SSI09** approached this from a population perspective, again due to their position as Director of B-R across a range of countries.

'You know, if you wanted to look at benefit-risk for malaria, which we're very deeply involved, I can fly samples of people from ten countries in Africa and bring them here, but I will learn much more to go there and sit where they are, because to them it might be self-evident some of these things, and they don't mention them but [laughter] you start looking and it's 'Hmm!' yeah. So again, this is something we need to learn to do, like, when it's appropriate or not. I think for conditions, for instance for psoriasis, it's essentially something we're focusing on in the Western world. I think we can bring patients to larger centres and do it; in other things it won't work, it really is not the right way to do this.'

*Theme VI: Motivation and ulterior motives of stakeholders*

Another theme of particular importance which emerged during phase I and which was clarified in phase II, was that of the motivation of stakeholders. Initially, the focus was on the motivation of patient advocates, however, as the study progressed this theme arose in a variety of difference contexts.

**Participant SSI01** described how patient advocates, at the EMA level, were often pre-selected based on their links with industry. They stated that ‘now there is probably one main reason (for their selection) is that, most of the patient association have links with industry, and so we probably chose only ones we know.’ This is an example of how pharmaceutical companies may influence who is involved in their B-R discussions.

**Participant SSI02** described those patient advocates who may not have the correct motives behind their involvement: ‘one thing you have got to guard against is the people that have got nothing else to do and just want to perpetually do this.’

**Participant SSI05** was clear in that all stakeholders have different motives, and this is not only applicable to patient advocates. They confirmed that:

‘I think sometimes it gets forgotten because, quite rightly, everyone has got different agendas, whether it’s to get a paper published or whether it’s to make profit on this drug or to be responsible for their stakeholders or to be careful about the NHS budget but, ultimately, it’s got to be about patient benefit, so it’s not just about patients just coming in at the table at a certain point towards the end, it’s about patients driving the agenda all the way through.’

**Participant SSI06** described how patient advocates may have their own agendas: 'Well, they've usually only got a personal hidden agenda. You know, not a professional, not a commercial' whereas **Participant SSI08** stated that 'it's quite clear that pharma. has almost an obligation to engage and so it's obviously going to be part of their compliance and their governance to do so.'

**Participant SSI09** presented their industry perspective: 'my view is it's as clear as day. This is coming, so you might as well embrace it, try to make the best of it, and [...] I don't have to be emotional about it, I just have to make sure I do it well. And if I do it well I do believe everybody will benefit, and those companies who do it better will have a competitive advantage over others.' The latter part of the statement was interesting. Not only did the participant confirm that this was the right direction to take, but they also presented the idea that this would give a competitive advantage over other companies who did not follow the same path. **Participant SSI09** continued: 'I have twenty people doing this now in this group, because I see this as the next big thing, and it's putting medicine back where it should be, which is centred on the patient. You don't do medicine for the money, you don't do the medicine for the prestige or the fun; you do it because you want to help patients. But the patient, (it's important to) ask them what they want, you know?'

Still, **Participant SSI09** also raised the possibility that 'my fear is that regulators will use this to confirm your bias. For example, this drug doesn't provide anything more. We're going to go to...', and that's why I'm so adamant that we need to do this pre-competitively: all agree on the rules so we don't come in twisting the truth.'

## **Discussion**

Research Phase II presented in Chapter V identified that patient involvement in B-R assessment was a current initiative which still posed challenges to even the most experienced experts involved in B-R analysis. Chapter V further contributed to the overall aim of this research of developing a framework to include patients. It was imperative to gain a deeper understanding of the perspectives of regulatory agencies, pharmaceutical companies and patient advocacy groups, as a framework which would ultimately be developed had to be acceptable to all relevant stakeholders. Thus, data was analysed so that the challenges faced by regulatory agencies and pharmaceutical companies could be further understood. To further develop the concepts and themes which were identified from phase I of the research, semi-structured interviews were completed with a number of key stakeholders. The objective of phase II was to (3) using qualitative semi-structured interviews, establish the opinions of representatives from pharmaceutical companies, regulatory agencies and patient advocacy groups, by undertaking thematic analysis of their views and opinions. In order to achieve this overall objective, several sub-objectives were established for research phase II.

The first sub-objective was to discuss the challenges of involving patients in B-R assessment with stakeholders. All stakeholders agreed that adequate representation of patients was an important topic requiring further investigation. Not only were patient advocates deemed to be an important stakeholder, they were also criticised by some; as the motivations of patient advocates were sometimes not always transparent. The involvement of patients was seen as tokenistic, yet it was also recognised that processes were in early stages of development and, overall, patient involvement initiatives were developing. The logistical challenges of involving patients were raised by several participants, and the logistics of running focus groups was also pinpointed as an obstacle which would need to be overcome.

The difficulty in identifying representative groups, or larger organised patients' organisations which were representative of the target patient was also a challenge. The objectivity of patients involved in B-R discussions was a theme which arose multiple times during phase I of the research in particular. Yet, although participants were quick to highlight a patient's objectivity, a number of participants in phase II gave examples, either, where their objectivity was questioned or where they had seen examples of a lack of objectivity of others; namely clinicians, regulatory assessors or patient representatives. Bias was described by all participants, yet all participants gave examples of bias by other stakeholders. Once this is recognised, the challenge of a patients' bias becomes less important. The key aspect is to recognise all potential sources of bias, wherever it arises, and then accept it, document it, and ensure transparency.

The second sub-objective was to develop solutions to the challenges of involving patients in B-R assessment. The method of involving patients was critiqued by participants and the general feedback by participants was that a qualitative focus group, undertaken alongside quantitative preference elicitation studies, could be a suitable way of gaining the patients' perspective, which could ultimately be used in B-R discussions. It was suggested the current model to involve patient advocates was no longer fit for purpose. Rich data was obtained to support the themes which were identified and verified during phase II. Themes describing adequate representation of patients, adequate methods for involving patients, the objectivity of patients, understanding and education, and insight into the patients' experience were all confirmed, analysed and verified. Subsequent to the completion of phases I and II, and to achieve the overall aim of this research a framework was proposed. This will be further investigated in Chapter VI.



## Summary

- All stakeholders agreed that the adequate representation of patients was an important topic requiring further investigation. Not only were patient advocates deemed to be an important stakeholder, they were also criticised by some; as the motivations of patient advocates were sometimes not always transparent.
- The involvement of patients was seen as tokenistic, yet it was also recognised that processes were in early stages of development and, overall, patient involvement initiatives were developing.
- The logistical challenges of involving patients were raised by several participants, and the logistics of running focus groups was also pinpointed as an impediment which would need to be overcome.
- The objectivity of patients involved in B-R discussions was a theme which arose multiple times during phase I of the research in particular. Yet, the objectivity of other stakeholders was also seen as inadequate.
- Examples of bias were identified. Moving forward this must be considered by all stakeholders. It is essential to recognise all potential sources of bias, wherever it arises.
- Solutions to the challenge of involving patients in B-R assessment included implementing an adequate method.
- Rich data was obtained to support the themes which were identified and verified during phase II. The adequate representation of patients, adequate methods for involving patients, the objectivity of patients, understanding and education, and insight into the patients' experience were all confirmed, analysed and verified.

**Chapter VI: Evaluation of the patients' perspective on their involvement in the benefit-risk assessment of medicines and a thematic analysis of the patients' experience**

## **Introduction**

Phase II of the research, presented in Chapter V, described the themes which emerged when participants from regulatory agencies, pharmaceutical companies and patient advocate groups were questioned about patient involvement in B-R assessment. Six overarching themes were emerged from the analysis. The most prevalent theme was the 'adequate representation of patients' followed by 'adequate methods for involving patients in B-R assessment,' 'objectivity of patients,' 'understanding and education,' 'insight into the patient's experience' and 'motivation and ulterior motives of stakeholders.' Data suggested that some patient advocates, especially those involved at the EU regulatory level, were perhaps not as representative of the relevant patient group as would be expected by stakeholders. The data collected in phase II suggested that stakeholders understand that patients should have an understanding and experience of the condition, to be able to represent others. Whether that experience is a result of them having the condition themselves, or perhaps because they care for someone with the condition, as a carer or relative.

Phase III was undertaken to confirm the themes which were identified and to identify any new themes which emerged directly by conversing with patients. Subsequently, this data would be used to generate a framework to involve patients in B-R assessment. Firstly, though, it was essential to gain an understanding of the different disease areas which would be investigated during phase III of the research. The FDA's Patient Focused Drug Development program contained information on several disease areas, however, due to resource implications, only a limited number of patient indications were selected for inclusion in the study.

### *Kidney disease and organ transplants*

Kidney donation and transplantation 'can be lifesaving, transformative, and restorative' for patients with nephrotic disease (FDA, 2016b). Many organs are recovered from deceased donors, 'but a substantial contribution of kidneys come from living donors' (FDA, 2016b). A successful organ transplant requires a strict pharmacologic regime in combination 'with non-pharmacologic management, before and after receipt'. (FDA, 2016b). Once the patient has received their transplant, clinicians focus on four main objectives: 'prevention of organ rejection by the recipient's immune system, treatment of the underlying medical condition, treatment of emergent complications of the immunosuppression (IS) regimen, including prevention and treatment of infections, and managing the adverse effects of the IS regimen.' (FDA, 2016b). Post-operative management is complex and serious illness can result due to a number of different causes, for example, 'viral, bacterial, fungal and other opportunistic infections.' Long-term pharmacologic treatments are required. They include 'induction immunosuppression with intensive combination regimens, maintenance immunosuppression with less intensive combination regimens, and additional medications for treatment of acute organ rejection'. (FDA, 2016b).

### *Cancer and curative therapies*

Cancer is a disease caused by uncontrolled growth of abnormal cells within human tissues, which, if left untreated, ultimately spread (metastasize) to other parts of the body (FDA, 2013c). Patients in the early stages of cancer may not experience many symptoms, and the cancer can grow for years before symptoms are felt. When symptoms do appear, they typically include shortness of breath, coughing, pain, weight loss, and fatigue (FDA, 2013c). Cancer treatments fall into two main categories.: (1) 'Therapies to cure, reduce the size of tumour, or control the spread of disease include surgery, radiation therapy, chemotherapy, and molecularly-targeted therapies' (FDA, 2013c). 'Chemotherapy drugs are designed to kill cancerous cells or stop them from dividing, while targeted therapies are drugs optimally used for specific individuals whose tumours have a particular molecular defect' (FDA, 2013c).

(2) Palliative or supportive care therapies are used to improve or manage symptoms of the disease or side effects of treatments; such as ‘supplemental oxygen, pain medications, steroids, and non-drug therapies such as breathing exercises’ (FDA, 2013c).

#### *Human Immunodeficiency Virus (HIV) and antiretroviral therapy (ART)*

Over time, the HIV virus attacks and gradually degrades the body’s immune system by depleting infection-fighting T-cells; ultimately resulting in acquired immunodeficiency syndrome (AIDS) (FDA, 2014b). The use of antiretroviral therapy (ART) to prevent viral multiplication is now recommended, reducing the likelihood of T-cell depletion (FDA, 2014b). ART involves a strict treatment regime, which can often require a ‘daily combination at least three medications’ (FDA, 2014b). ART is not curative, however, with careful management of the patient’s viral load there, is not only a reduced risk of ongoing transmission, but also a reduced risk of progression to AIDs (FDA, 2014b). Still, an important consideration of ART therapy are the short and long-term side effects of treatment, which can greatly impact the patient. ‘Short-term effects include diarrhoea, nausea, headache, and sleep disturbances, among others’ whereas ‘potential long-term effects can include body changes (e.g., fat build up or depletions in particular areas of the body), kidney, liver, heart or bone side effects, and others’ (FDA, 2014b). Without strict adherence to the ART regimen, drug resistance can occur which may ultimately result in a progression to AIDs.

#### *Psoriasis and psoriatic arthritis*

The clinical presentation of psoriasis, a chronic inflammatory disease, often includes areas of red, thickened, scaling skin that are itchy or sore. The most common type, plaque psoriasis, is ‘characterised by inflamed, red skin covered with silvery white scales. The patches may itch and burn and can appear anywhere on the body, but often on the elbows, knees, scalp, and lower back’ (FDA, 2016a). Psoriasis has been shown to be closely linked with psoriatic arthritis and therefore patients’ often present both skin and joint manifestations (FDA, 2016a).

Psoriatic arthritis 'typically manifests as joint pain, stiffness and swelling' (FDA, 2016a). 'There is no cure for psoriasis; however, there are several treatment options that aim to reduce and manage symptoms and improve the quality of life' (FDA, 2016a). Topical treatments, phototherapy and oral and injected medications are all used to treat psoriasis and psoriatic arthritis. Medications include 'methotrexate, acitretin, cyclosporine, apremilast, and biologics, such as etanercept, infliximab, adalimumab, ustekinumab, and secukinumab' (FDA, 2016a). In addition to medications, changes in lifestyle, 'such as diet and alternative therapies, are also common components of psoriasis treatment regimens' (FDA, 2016a).

It was important to gain an understanding of disease areas which were to be investigated in phase III. To further develop the concepts and themes which were identified from the survey data, semi-structured interviews were completed with those participants who wished to participate in phase II of the research. The objective of phase III of the research study was to (4) using focus groups to disclose the views of patients, identify the patient's perspective; to include an insight into their condition and their opinions on patient involvement in benefit-risk assessment discussions. In order to achieve this overall aim, several sub-objectives were established for phase III of the research.

### **Sub-objectives**

- Evaluate the patient's perspective on their involvement in the B-R assessment of medicines.
- Obtain rich data on the themes which were generated in previous phases of the research.
- Compare and contrast the perspective of patients with different diseases.

## Methods

### *Review of FDA's Patient Focused Drug Development Disease-specific meetings*

In addition to the ongoing literature review, which focussed on the benefit-risk assessment of medicines, an ongoing review was undertaken on the FDA's Patient Focused Drug Development 'Disease-Specific Meetings'. This was completed to prepare for data collection, and later to compare and contrast the data collected in phase III of the research (FDA, 2013c, 2014b, 2016a, 2016b)

### *Patient and public involvement (PPI) review*

As a study investigating how patients could be incorporated into a benefit-risk assessment framework, it was essential to start the research as it meant to go on: to include patients in the study design and theory generation. The Patient and Public Involvement Group at Guy's hospital were invited to review the study documentation. Three patients responded to the request and their comments were included in the study application.

### *Development of the focus group interview schedule*

A schedule of questions was prepared (Appendix VII). Questions were based around existing methods of including patients in B-R assessment as well as the challenges of involving patients and potential solutions. The questions were divided into three topics:

- Topic 1: Disease overview
- Topic 2: Patient perspectives on current approaches to treatment
- Topic 3: B-R assessment methodology

### *Local applications for approval*

Firstly, agreement was sought from those departments that would ultimately be involved in the study at Guy's and St Thomas' hospitals: the clinical research facilities and the following clinics: renal dialysis, oncology, rheumatology, and HIV. The set-up of phase III of the research commenced only after agreement had been sought from the lead consultants within each clinic.

### *Integrated Research Application System (IRAS) application*

An application was prepared using the integrated research application system (IRAS). The IRAS form was finalised, signed electronically by the chief investigator and sponsor; and submitted to the 'NRES Committee South East Coast – Surrey' research ethics committee for ethical review.

### *Study set-up*

The study was presented to the CRF review board of the clinical research facilities, and approval was obtained to complete the data collection and analysis within the clinical research facilities. A central study master file was maintained, which contained all study-related documentation.

### *NHS Research Ethics Committee and Health Research Authority applications*

An NHS Research Ethics Application was prepared in line with the requirements of the Health Research Authority (HRA) and the national research ethics committee.

### *Ethical implications*

The main ethical issue to highlight to the REC was interviewing patients during patient focus group meetings about how their medical condition affected them. There was potential that this could be distressing for some people, for example the pain they experienced or the way in which their treatments affected them, such as drug side effects. This may involve divulging issues of a sensitive nature, so these issues had to be approached carefully by the thesis author. It was made clear to all participants that they were free to discontinue at any time and that they did not need to divulge anything that they were not comfortable sharing. In addition, the patient focus groups were to be recorded, therefore some people may not have wished to discuss personal issues while being recorded.



#### *Research ethics committee meeting*

The researcher presented the protocol, study documentation and the focus group schedules to the research ethics committee, who requested minor amendments and clarification. Once REC approval was received, the Health Research Authority (HRA) was also approached. Approvals were received and copies are stored in Appendix VIII.

#### *Research and Development (R&D) approval*

Once the REC and HRA had approved the study, the study was approved by the R&D department at Guy's and St Thomas' NHS Foundation Trust (Appendix VIII). Thus, recruitment could commence.

#### *Recruitment*

Patients were identified from clinics by doctors or research nurses based within each department. Patient medical records were reviewed before patients were approached by the clinical team who then advised the researcher who was eligible. The study was introduced to eligible patients during their routine clinical appointments by doctors or nurses responsible for their care. The doctor or nurse gained consent from the patient to be contacted by the researcher. The researcher sent an invitation letter and Patient Information Sheet with a tear off slip (and prepaid stamped addressed envelope) which patients sent back if they were interested in being contacted. Once the patient replied, the researcher booked the participant in to attend an appropriate patient focus group (depending on the condition that they had).

#### *Focus group logistics*

The meeting room was booked, the room prepared and the patients were informed of the date and time of the focus group. The researcher arranged for a taxi if the patient requested one, otherwise patients made their way to the meeting as agreed.

### *Consent*

Patients were consented on arrival, after confirming they were happy to move forward with the study. They signed the consent form while the researcher countersigned. A copy of the consent form was filed in the study file, one was added to the patient's medical records and a copy was given to the patient.

### *Focus groups*

Braun and Clarke (2013) describe how 'using a group discussion format has become increasingly popular way to collect data from participants.' The researcher leading the discussion is called a 'moderator', rather than an 'interviewer' (Braun and Clarke, 2013). This is because the moderator is not asking direct questions as with an interview, although some questions of course are involved, but rather they lead a discussion; which is hopefully generated between participants (Braun and Clarke, 2013). 'Social interaction among group members is central to the method; it's what distinguishes focus groups from methods like interviews or surveys' (Braun and Clarke, 2013). They are potentially complex social situations, as participants interact with each other to make comments, ask questions and generate discussion (Braun and Clarke, 2013). It was planned that each focus group would include up to five people at a time, based on both feedback received from the Patient and Public Involvement group at Guy's hospital, and also that 'smaller groups (three – eight participants) work best in gathering a rich discussion' (Braun and Clarke, 2013). Refreshments were served at the onset of the focus group, to relax participants and for the moderator and participants to get to know each other, prior to the data collection stage.

### *Recordings, transcription and coding of themes using QRS\*NVIVO*

After data was collected via audio recordings and all interviews were complete, data was prepared for analysis, using orthographic transcription. The transcripts were uploaded to QRS\*NIVO and the qualitative data were coded and the data allocated to nodes (theme categories).

Participants were given the opportunity to review transcripts and the emerging themes, to ensure the data was an adequate representation of their opinions. This process, known as ‘member checking’ is a form of quality control.

**Figure 6.1 - Screenshot of coding using QRS\*NIVO**

The screenshot shows the NVivo Pro interface with a list of nodes. The nodes are organized into a tree structure on the left, and a detailed table is displayed on the right. The table columns are Name, Sources, References, and Created By. The nodes listed include Adequate representation, Methodology, Understanding, Insight, Treatment, Patient acceptance, Disease progression, Methodology, Patient participation, Patients' view on representation, Demographics, Emotion, and Objectivity.

Name	Sources	References	Created By
Adequate representation	14	68	PIC
Methodology	12	57	PIC
Understanding	13	46	PIC
Insight	14	38	PIC
Treatment	5	17	PIC
Patient acceptance	5	16	PIC
Disease progression	2	5	PIC
Methodology	1	3	PIC
Patient participation	1	2	PIC
Patients' view on representation	1	2	PIC
Demographics	2	2	PIC
Emotion	1	1	PIC
Objectivity	10	29	PIC

### *Thematic analysis and generation of themes*

Thematic analysis, coding and the further validation of themes already identified was completed. After the transcription, it was important to read and to become familiar with the data, making note of items of potential interest. The next stage was to undertake coding, or organising the data into themes, before deciding upon which themes and sub-themes were prevalent across the dataset and which were of most importance. The themes identified were used to develop theory in phase III.

## **Results and thematic analysis**

Once the coding and analysis was complete, the data held on QRS\*NIVO was reviewed and compared against those data collected in phase II. After analysis, the following themes continued to emerge, but this time from conversations with patients themselves. The themes were:

- Objectivity of patients
- Understanding and education
- Insight into the patient's experience
- Motivation and ulterior motives of stakeholders

### *Participants*

After being approached by their consultants, fifteen participants agreed to participate in the focus groups. Yet, on the days of the focus groups several participants decided they no longer wished to participate and did not turn up, therefore, only 8 participants moved forward into phase III (53%).

Of the 8 participants whom participated in the focus groups and completed phase III of the research, 2 participants (25%) were recruited from the renal clinic, 2 participants (25%) were recruited from oncology, 2 participants (25%) were from the HIV department and 2 participants (25%) were recruited from rheumatology. All participants were allocated a pseudonym to protect their identify. The participants who participated in the focus groups are displayed in Table 6.1.

**Table 6.1 – Focus group participants**

<b>Participant's Pseudonym</b>	<b>Patient indication</b>	<b>Primary therapy</b>
George	Previous renal failure (post-transplant)	Immunosuppressants
Robert	Previous renal failure (post-transplant)	Immunosuppressants
Peter	Solid tumour	Phase I chemotherapy
Mary	Solid tumour	Phase I chemotherapy
Henrietta	HIV	ART
Charlie	HIV	ART
Phil	Psoriatic arthritis	Phase III monoclonal antibody
Susan	Psoriatic arthritis	Phase III monoclonal antibody

*Thematic analysis and the clarification of emerging themes*

After analysis, four themes previously identified continued to emerge. Throughout the focus groups, similar themes arose and also new information was identified. In addition to those candidate themes which were identified in phase II of the research, any new themes or concepts which emerged during phase III were also documented and investigated. The themes which were identified and verified will now be presented. A description of theme will be presented as will examples of how the theme emerged from the data, by quoting participants and presenting what they said and how they said it. Themes which were most prevalent are described first and any sub-themes which were identified are also described.

*Theme III: Objectivity of patients*

The objectivity of patients was a concern for a number of stakeholders during phase II of the research. Yet, participants in the focus groups appreciated this risk. **Peter**, a participant from **Focus Group 2 (Cancer)** used the term 'objective' without any prompt from the researcher, indicating he was well aware of this potential issue:

**Peter** To be honest with you, trying to be objective, I don't find it impacts me at all really, because the impact it would have...I have a part-time job, I work three days a week, I work Wednesday, Friday and Sunday. So, it's not impacting my work, because I come on a Tuesday, it's not that onerous, I'm not sitting in draughty corridors, you know, I'm talking about the, sort of, nuts and bolts of the treatment. Obviously if I were working, I would say, well I've got to come...you know, one day a week I've got to come up here.

**Focus Group 2 (Cancer)**

**Peter** also commented on emotion, which also supported that it appeared he understood the importance of objectivity, when he said:

**Peter** To be honest, through this data, because I think at that stage, when scientists and clinicians are doing that, evaluating, whatever, the last people you want in there are politicians and people with, like, an emotional interest in it. Because you need the judgment of Solomon, don't you, really?

**Focus Group 2 (Cancer)**

**Phil**, a participant from **Focus Group 4 (Psoriatic arthritis)** also raised the issue of bias, especially when something may be to a person's benefit, highlighting the theme of 'motivation' at the same time.

**Phil** It's hard to say when the medicines have had such a positive result, the bias, you can't really see the bias because it's obviously, it's gonna benefit you. But if there was something which was a bit, "Oh I'm not sure whether it works on 50% of the people," so the bias would be more.

#### **Focus Group 4 (Psoriatic arthritis)**

Later, **Phil** also highlighted how all people have some element of bias:

**Phil** That's what I said early on, because we're all gonna be bias to it because it's got such a good result, to the point where if you are getting side effects you're not gonna make much of a big deal out of them because you've got such a good benefit of the drugs.

#### **Focus Group 4 (Psoriatic arthritis)**

#### *Theme IV: Understanding and education*

The theme of understand and education was another concern for stakeholders during phase II of the research. Examples did exist where patients may have misunderstood certain elements, however many patients came across as proactive and eager to learn about their condition, their treatment and how they could modify their lifestyle in order to improve their lives.

During **Focus Group 3 (HIV)**, **Charlie** described the challenges he faced of dealing with not only HIV but also diabetes too. On this subject, he questioned the understanding and education of all stakeholders, namely clinicians.

**Charlie** The HIV doctors will not tell you it's the medication but when I went to Pain Management, the consultant told me it's because of the HIV medication.

#### **Focus Group 3 (HIV)**

**Charlie** was frustrated by the mixed messages he had received from different consultants about adverse events he had experienced. Charlie described how, after not receiving a 'straight answer' from his consultant about whether ART and diabetes had some relationship, he used Google to investigate ART side effects himself:

**Charlie** Basically I got told off for doing it because I'm not supposed to do that because one could get called a hypochondriac and take everything on board and I said, "Well I'm not stupid." Anyway, I got GlaxoSmithKline actually published a booklet about HIV and diabetes in line with positive, the American version of positive UK and a positive life in America.

**Moderator** Right.

**Charlie** So I wrote to the man over here and I said, "Why isn't this kind of booklet being published over here?" "Well it's not down to us, it's down the Government." So, I wrote to the Government and they said, "Well it's not down to us." I'm thinking, "Then who is it down to?" As I said, when I gave that talk a couple of minutes ago where the doctor said, "Well we've known about the side-effects since 1990." I said. "That's terrible, because there are some of us out there now that our lives are totally ruined."

### **Focus Group 3 (HIV)**

The patients' understanding around risk perception and risk understanding was also discussed. **Charlie** described how he felt he wasn't being listened to when he reported adverse events.

**Charlie** At the end of the day you've obviously been given that information and that must probably be... Do you know what I wouldn't have gone through what I had gone through but then again in one sense what I have gone is literally what I'm doing



now. So, some good has come out of it. Like I said, the side-effects...you try and tell your HIV consultant. "Well it can't be the antivirals." I'm thinking yeah, but we're not stupid. Of course, the medication is causing problems.

### **Focus Group 3 (HIV)**

During **Focus Group 3 (HIV)**, **Henrietta** argued she wouldn't participate in research because of the perceived risks.

**Henrietta** How would they know (what the risks are)?

**Moderator** How would they know? They don't know.

**Henrietta** Because if you remember this, what was it again, that tablet they used to give to women when they were pregnant...?

**Moderator** Oh, yeah, thalidomide.

**Henrietta** Did they know? No.

It was interesting how an event so long ago still has such damaging effect on the perception of research as a whole. It underlines the importance of education, to assure patients that such events are, in fact, incredibly rare. The conversation continued:

**Moderator** Do you think we all focus on risks too much or do you think it's important that we do?

**Charlie** No, I think it's important that you do.

**Henrietta** Hmm, it's important.

**Charlie** I don't think everybody weighs the risk up and then says, 'no, I'm not going to take it.' But, I think it's just having that knowledge. Like I said, if I had been told I would get diabetes, at least I would have known what I was dealing with.'

### **Focus Group 3 (HIV)**

**Charlie's** point was valid. When people are well informed and if something negative does happen, they are more likely to accept it.

#### *Theme V: Insight into the patient's experience*

This theme was widely expanded during the focus groups, which would be expected. Thus, the theme was coded into two sub-themes: (1) disease progression and making lifestyle changes and (2) treatment and medication.

**George**, from **Focus Group 1 (Renal)**, was diagnosed with kidney disease in his twenties. He remembered the day when he first accepted that his condition was deteriorating.

**George** I remember one day I was going to a meeting and I was crossing through Covent Garden and there was a guy walking towards me. He was obviously a bit the worse for wear. He was really quiet, and, well, he looked like he had been up all night. As he came across my path he looked up at me and said, "Gaud, you look bloody awful, mate." I thought, oh great, thank you very much. And I did, I just felt exhausted all the time.'

### **Focus Group 1 (Renal)**

This real-life example was incredibly impactful. It is an example of why the patient's perspective is so important, yet, this in itself presents a risk where other stakeholders may lose their objectivity, due to the emotive stories presented to them. **Robert**, the second patient who attended **Focus Group 1**

**(Renal)**, had a similar real-life story to present when he noticed that he was unable to do as much at the gym as he could previously:

**Robert** I thought to myself, “I’m struggling now.” Things I used to use, twelve or fourteen kilos with, I was back down to about nines and eights, and I thought that this is getting probably because of my symptoms. Anyway, a month before my operation I stopped going to the gym totally, because it was just silly. I struggled to walk round there, which is about a mile. That’s my warm-up is walking to the gym.

**Focus Group 1 (Renal)**

**Robert** also described the months leading up to his renal transplant.

**Robert** I was ballooning with the water but nothing else really so I was getting really sort of gaunt at the top and sort of really ballooning down there at the bottom end. But, when all that corrected itself I found that I was still...I was about a stone lighter than so yeah, I was yeah about six, seven kilos lighter than I was when I... Before I had the op. And I thought “Well that’s good” because I really always wanted to lose that and I’ve managed to keep that off and although sometimes I’ll go up a kilo a kilo and a half I know that if I just watch what I eat for a week it will come back down again.

**Robert** displayed real emotion on discussing the moment he discovered his wife’s kidney was a match:

**Focus Group 1 (Renal)**

**Robert** When they said it, I was almost... When my wife told me that I could have one (a kidney) and it was really good match, I went outside and cried and I’m feeling well enough now.

**Focus Group 1 (Renal)**

After asking about how he considered his post-transplant medication, Robert confirmed he didn't even think about it.

**Robert** As far as I was concerned, I don't think it made any difference to me. The tablets I took were for the conditions that I was taking them for.

### **Focus Group 1 (Renal)**

**George** described how his perspective changed when compared the time before and after his transplant.

**George** Pre-transplant, [...] you're ready to give almost anything a go. Post-transplant, when things are going very well, I think it would be much more difficult a decision. I know there is this talk that they've been looking at doing a trial of taking people off immune suppressants altogether because some people have had to come off for other reasons'

This is a good example of 'insight' but it also demonstrates the 'objectivity of the patient.' There is a risk that patients 'will give almost anything a go,' therefore this is a risk in B-R discussions, as objectivity is essential. **Peter**, from **Focus Group 2 (Cancer)** described how he'd already experienced sensitivity since commenced his chemotherapy for a solid tumour.

**Peter** (I had his drug) I still haven't got the feeling back in my fingertips 100% now, and my toes. That cup, you know, *(pointing to a plastic cup)* if you put a temperature on it, it would be whatever, but if I pick that cup up, when I was (on the drug), that would slightly burn through coldness.

**Moderator** Really? Sensitivity?

**Peter** Yeah. Anything out of the fridge, it would be like holding a kettle, because your fingertips go numb. When you drink, your throat, it doesn't swell, but it feels like it's swelling, and it feels like you can't swallow - and like I say, that is a new beneficial drug. Now if this, in any way, can replace that sort of thing, that would be stunning. If me taking this forms part of information that stops one person feeling like that, it would be...yeah, so worth it - yeah. So, yeah, part of it is: I hope to god it helps me. But if it doesn't, I would take some comfort, not insubstantial comfort, from it helping the general picture, even if it was negative to positive, to be honest.

**Peter** went on to describe the environment where he received his chemotherapy, and now they impacted on the way he felt.

**Peter** For a clinician, or whatever, a Carer, the bigger picture must be helpful. You know, I've been fortunate so far, touch wood, I've been in rooms and I've been eight times out of ten the youngest person in there. So, consequently, I haven't had the complications that other people have, and I've seen some people privately struggle with sickness during their treatment. I think the treatment is geared up to plug you in, you know, in the nicest possible way, I don't mean...

**Moderator** Yeah, I know.

**Peter** I would not sit here and go: right, it's horrible this, it's horrible that. But there's a certain impersonality to it, because a nurse has gotta get through the day, you've just gotta treat people. But maybe this sort of thing would...

**Moderator** Consider people's thoughts and feelings a bit more, makes it a bit more personal?

**Peter** Yeah. I mean, maybe some guys...guys, people refuse treatment and the reason, I think it's irrational, and that could be avoided simply.'

### **Focus Group 2 (Cancer)**

**Mary** described how she hadn't really had any symptoms from her cancer, however, the treatment was far worse.

**Mary** I never really had symptoms, it was just a fluke that they found it really, so I suppose chemo's been the worst.

### **Focus Group 2 (Cancer)**

Yet, as **Mary's** disease progressed, she did notice symptoms develop.

**Mary** It's breathlessness as well with me, but that is easing slightly. I'm not saying I'm back to normal, but I can do a little bit more and then sit down. I can do something for a little bit longer period now then, so it must be easing off slightly. I've had three lots of chemo. The first two were bearable, but the third one, I'd only had a couple and then before Christmas, I was admitted to hospital and I had sepsis and pneumonia and I was isolated for a couple of weeks. When I started it again, instead of having 100% of it, they dropped it to 80%...

**Moderator** Reduced dose?

**Mary** Yes, and well, I was still sick and that, but it was bearable.

### **Focus Group 2 (Cancer)**

**Mary** described the sickness she'd experienced as part of treatment. She mentioned her family were always there to watch over her.

**Mary** But, it made me laugh really, because they've always said I'm very loud when I'm being sick, you see. So, my husband rang my son on the train and he said, oh how's mum, so he said, well, she's been sick but she's not very loud this time. So, we always laugh about that.

### **Focus Group 2 (Cancer)**

It was positive to hear that **Mary** was able to use humour to deal with her situation. **Charlie**, in **Focus Group 3 (HIV)**, had strong opinions about the 'generation below' referring to the younger generation.

**Charlie** But, it is scary that this recent thing about the generation below is that could be HIV on medication. That they see it as, "Oh our lives are going to be wonderful." Yeah, they might be for a shorter time but you're looking at the long-term and that what's scares me.

**Moderator** Oh really?

**Charlie** I feel like it, yeah, I feel like just handing our sweets and I've said that before. I've said it's like the doctors couldn't decide...doctors are handing out packets of Smarties and they're not taking into consideration the side-effects. I'm thinking well fine and like I said at the end of the day, the HIV consultants do need to be responsible because they're the ones that are handing

out the medication. If a patient goes to them and says it's causing A, B, and C, they should take it more seriously.

### **Focus Group 3 (HIV)**

**Henrietta, Focus Group 3 (HIV)**, described her experience of having an eye infection. After complaining several times, she described her experience:

**Henrietta** Nothing happened, until I got so upset I started crying. They called in the eye specialist and I was [...] treated...well, they said I had shingles in it, so I was treated. I've had a glaucoma removed two times. It didn't work, until, in the end, I just decided I cannot take it anymore, so I had it removed (her left eye).

### **Focus Group 3 (HIV)**

**Susan, in Focus Group 4 (Psoriatic arthritis)**, described her diagnosis and the experience she had over the years.

**Susan** I've had psoriasis for, I think about, 'cause I'm quite old, so I've had it about 40, 40 odd years. And initially it wasn't, probably even more than that, it wasn't really diagnosed then you know, it was sort of like a creeping eczema I think they thought it was, and then it was eventually diagnosed, and I had various treatments. And in the last, I think two years, going to rheumatology I was referred to rheumatology because I'd been complaining for a long time that every time I got out of bed my feet were like a pair of flippers, you know, I couldn't get up and down the stairs comfortably, I could walk but it was uncomfortable. My hands for a long time had felt like cotton wool and they'd ache as well, and I couldn't open things properly, they were very, very, woolly, and I was then diagnosed with psoriatic arthritis. Is that enough at the moment?



**Moderator** Please continue...

**Susan** It was and, you know, at the moment when you think back all those years I've looked like a lizard really, you know, I could cry sometimes when I think now, "You're clear," and people don't realise, they treat you like lepers, you know, I've had many people in the past saying, "Is it catching?" You get, that's quite common, it's quite common, you get, "Eurgh what's that?" And it's awful really. [...] and it does affect you mentally.

#### **Focus Group 4 (Psoriatic arthritis)**

**Phil** and **Susan** compared their experiences in **Focus Group 4 (Psoriatic arthritis)**.

**Phil** I was kind of fortunate that most of my psoriasis wasn't really visible.

**Susan** But, it doesn't matter whether it's visible or not because you've still got pain, whether it's externally or internally, it's there and you feel just as rotten, whether you can see it or not.

**Phil** Yes that's right.

**Susan** And, it does affect you mentally.

**Phil** You, kind of, forget, well for me anyway, the way the medicines for me I kind of forget how bad it was and I've...

**Susan** Yeah, I can imagine and I mean, since we started this programme, I can't believe how quickly it actually changed. It wouldn't completely go, and some on the rear end, so it wasn't completely gone but it was much, much better than what I'd had. 'Cause psoriasis is a funny thing anyway, you know, you might

be completely covered, or relatively, more than 50% of your body, but it can go away and just come back somewhere else that it hasn't been before, so you're constantly not sure what's gonna happen next, and having the methotrexate I think with this secukinumab has worked quite well really.

#### **Focus Group 4 (Psoriatic arthritis)**

**Phil** and **Susan** compared their experiences of treatment and they also commented on how positive they found the focus group experience.

**Susan** Even if they had two patients, it's better than one patient.

**Phil** Yeah, 'cause even just between us two it sounds like there's quite a different, you have very different symptoms to me, and the medicines working slightly different by the sounds of it, but we're getting the same results.

#### **Focus Group 4 (Psoriatic arthritis)**

##### *Theme VI: Motivation and ulterior motives of stakeholders*

The motivation of patient involvement was a particularly interesting theme when viewed from the patient's perspective.

**Peter** The thing is, once you start the trial, you're on it for your own benefit, initially, but then obviously it works or it doesn't work, so the general use of the trial, kind of, becomes more important.

#### **Focus Group 2 (Cancer)**

**Mary**, the second patient who participated in **Focus Group 2 (Cancer)**, had a similar perspective.

**Mary** Well, (a) hoping it would help me and (b) for people in the future. [...] I like to help other people but as I say, I suppose you put yourself first don't you, you know, hoping it will help you.

### **Focus Group 2 (Cancer)**

**Charlie** had a lot to say about how being an early user of ART, in **Focus Group 3 (HIV)**.

**Charlie** I think what comes to mind will be...because we've already done that, we already participated. So, really, we've helped society as such. People that are utterly the new patients, they are benefitting from what research they've done on us [...] It (helping others) might make us feel better, but the psychological side of it, we might be taking the medication, and we're not dropping dead, but the psychological side of it is that you've got to take your tablets every day, you've got to inject yourself. Then socially you've got to help other people to understand it.'

### **Focus Group 3 (HIV)**

**Phil** and **Susan** discussed their perspectives on their motivations during **Focus Group 4 (Rheumatology)**.

**Phil** I think personal first, because I was...I'm self-employed, I make furniture and some of the job's very physical so I'm lifting all the time, and I was starting to worry how long I was gonna be able to do my job for because of the way my psoriasis, the arthritis was going, that was gonna stop because I started to lose strength in my grip and lifting things, I could still lift but it was more difficult or painful, so yeah...and on your feet all day as well.

**Moderator** Yeah, and yourself?

**Susan** I think I reiterate, personal really. Purely from the point of view, if I was still working, 'cause I'm retired now, but you want to feel...I mean I had an office type role, manager role, and you want to feel comfortable when you're with other people, so it's a bit of a selfish reason.

**Moderator** It's not selfish at all, not at all. So, do you think that's more how it affects you physically, or do you think that's more how it affects you mentally, socially as well?

**Phil** Yeah, it would have been...

**Moderator** Or is it a bit of both?

**Susan** I mean there's an element of both with mental, because if you've got a, as you both know, if you've got a problem, an illness, or whatever you like to call it. If you've got an illness and it's causing you problems it can sometimes make you grumpy, you don't wanna communicate, you start worrying about what it's doing to you and then eventually it's what you're doing to other people, so you know it encompasses a number of things really, but really it's the personal thing, if you feel good everything's rosy.

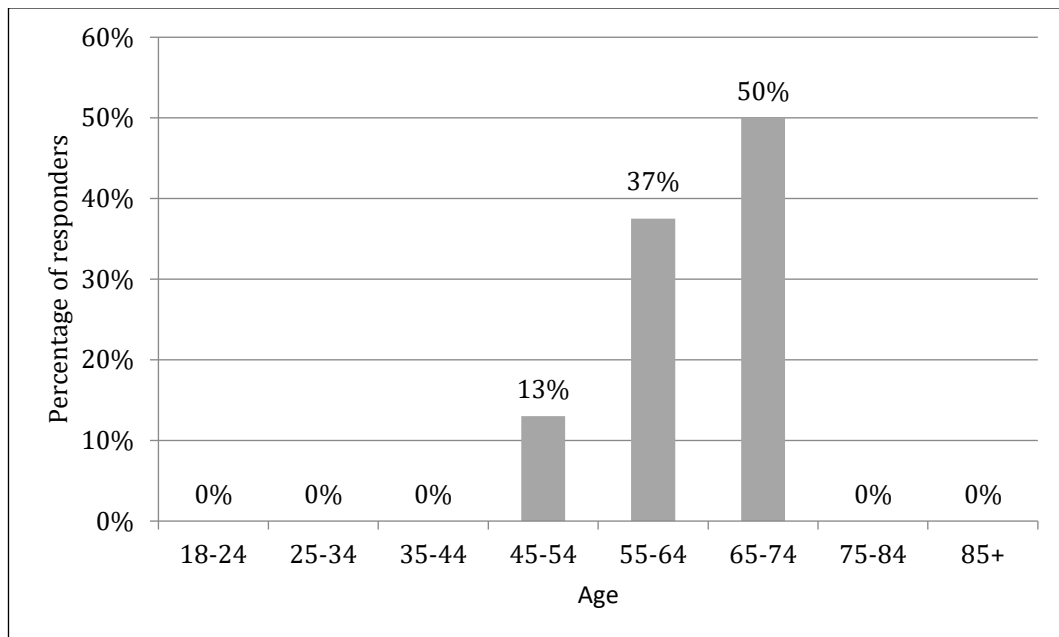
**Phil** There is the social side of things that people, if it's not a visible disease, people don't really have any sympathy for you.

**Susan** No, course they don't.

#### **Focus Group 4 (Psoriatic arthritis)**

*Demographics characteristics of the participants*

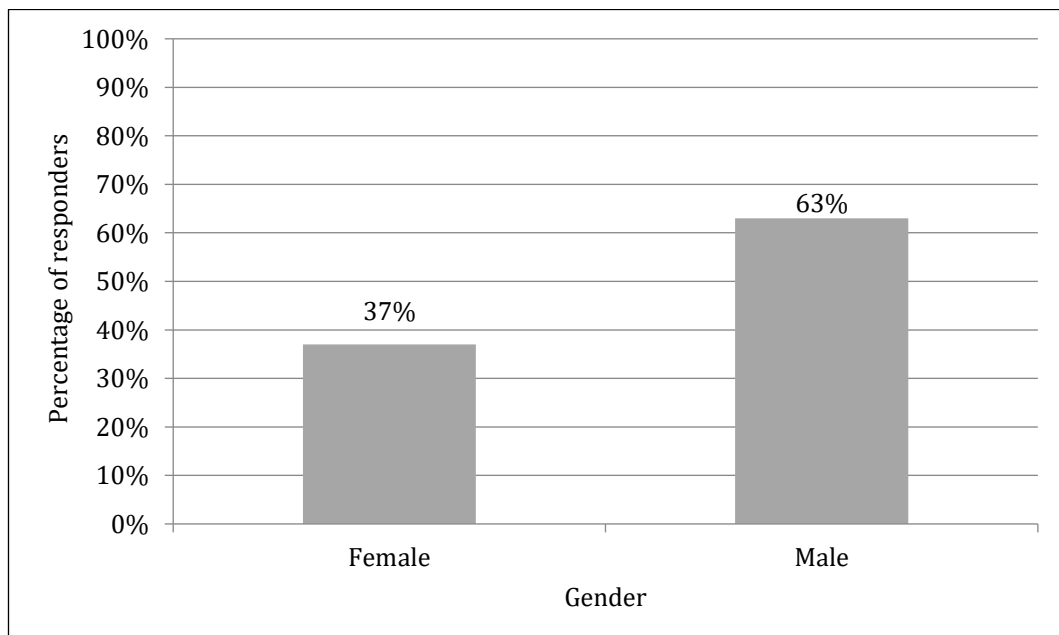
**Figure 6.2 – Age range of focus group participants**



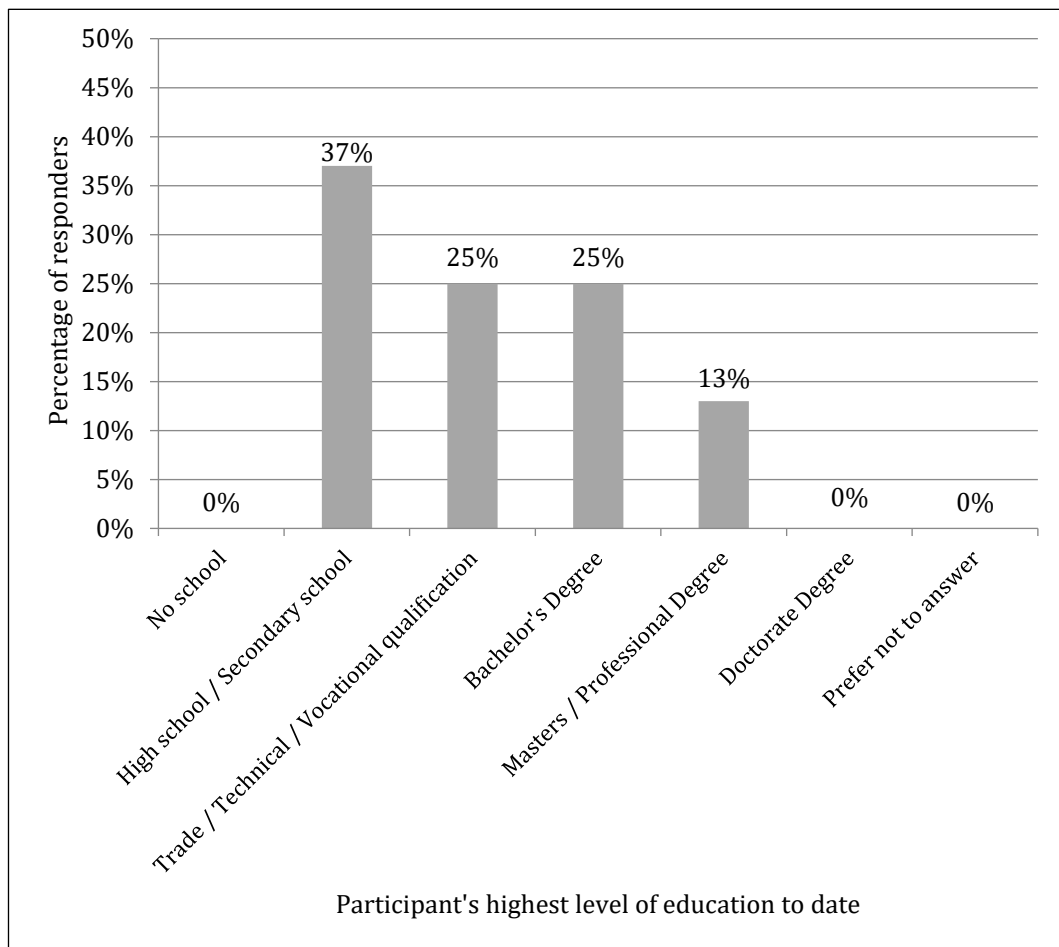
**Ethnicity of focus group participants**

Six participants described themselves as ‘White British,’ one participant ‘African-Caribbean’ and one participant ‘dual heritage’ (of White British and African -Caribbean descent).

**Figure 6.3 – Gender of focus group participants**



**Figure 6.4 - Highest level of education (Focus group participants)**



When comparing the demographics of the participants from phase I and compare them against those participants who took part in phase III, there is a clear difference. Regulatory agencies, pharmaceutical companies and patient advocacy groups are notably staffed by white, educated, middle class individuals. The patients recruited for phase III were from a range of educational backgrounds and the group was more diverse (notably that no ethnic minorities were represented in phase I and II).

## **Discussion**

Through the focus groups, rich data was obtained on the patients' perspective on their involvement in B-R discussions. The objective of phase III of the research study was to (4) using focus groups to disclose the views of patients, identify the patient's perspective; to include an insight into their condition and their opinions on patient involvement in benefit-risk assessment discussions. In order to achieve this overall aim, several sub-objectives were established. The first sub-objective was to evaluate the patient's perspective on their involvement in the B-R assessment of medicines. This was an interesting element of phase III, as patients with different diseases definitely had unique perspectives. It was surmised that even patients with the same disease would be willing to accept different levels of risk depending on their prognosis, adding even more complexity to ensuring an adequate method of patient selection.

The second sub-objective was to obtain rich data on the themes which were generated in previous phases of the research. Rich data were obtained; especially regarding Theme V: Insight into the patient's experience. Patients provided evidence for both sides of the argument. On one side, Peter demonstrated his ability to remain objective, even while undergoing the challenges associated with chemotherapy. Charlie, on the other hand, had a strong personality and, although he made some good points, his inherent bias was also apparent. Patients demonstrated their ability to understand B-R, whatever their education level, yet, Henrietta highlighted the point that patients can be influenced by previous negative press, such as the coverage of the thalidomide disaster. Mary was able to remain positive, even when she was experiencing terrible side effects. Phil and Susan offered a unique experience for the researcher, when they were able to compare and contrast their individual experiences regarding their secukinumab treatment. This had particular meaning for the researcher, which will be further described in Chapter VII.

The third subobjective was to compare and contrast the perspective of patients with different diseases. It was clear that different patients had lots in common. It did appear that what they were prepared to accept with regards to treatment depended on the severity of their disease and the patient's prognosis. Patients with severe disease would be more likely to accept higher risks than those with less severe conditions, which is not surprising. The patients' accounts described during phase III were all interesting and unique experiences which demonstrate the importance of the patient's perspective, and how insight in the patient's experience would contribute greatly to B-R discussions. The proposed framework, developed as a result of this PhD research, will be presented and critiqued in Chapter VII.

### **Summary**

- Patients are able to offer a unique perspective into their condition, their treatment regimen and their overall outlook with regards to their treatment decisions.
- With regards to the objectivity of patients, evidence was provided for both sides of the argument.
- Patients can be influenced by other sources such as negative press, therefore adequate training and education is essential.
- Different patient groups offer completely unique perspectives, depending on their condition, its severity and the treatment which they're undergoing.
- Patients remain robust in their mission to face their challenges and would be important partners in future B-R initiatives. Still, Patients with severe disease could perhaps be more likely to accept higher risks than those with less severe conditions.



# **Chapter VII: General discussion and conclusions**

## **Introduction**

It is recognised that when considering those personnel involved in the B-R assessment of medicines, there are several important stakeholders; including pharmaceutical companies and regulatory agencies. It is also accepted that the inclusion of patients is essential for understanding what is most important to them with regards to the disease and treatment. The crucial question raised from this PhD research, however, was should patients be involved in B-R assessment? Indeed they should, yet stakeholders must recognise the risks and challenges which emerge from their inclusion.

When this programme of PhD research commenced in 2013, multiple stakeholders were in the process of publishing their plans to develop methods for involving patients in B-R assessment. By the end of 2017, several projects had been completed, including the FDA's Patient Focused Drug Development Initiative. Still, a framework, developed solely for the purpose of involving patients in B-R assessment was at the time of writing this thesis still not forthcoming. This was due to the complexity of the topic itself and the different approaches available. The fact that different organisations were implementing varying strategies indicated there was an opportunity to make a novel contribution to this topic. Both regulatory agencies and pharmaceutical companies are under increasing pressure to improve transparency and accountability with regards to their internal processes regarding B-R. By involving patients in these initiatives, they have an opportunity to develop B-R systems and processes for the better. A survey conducted with regulatory agencies, pharmaceutical companies and patient advocacy groups confirmed that one major challenge for stakeholders was the lack of an internationally accepted, validated framework. The ultimate aim of this research was to describe, analyse and synthesise study data to ultimately propose a semi-quantitative framework for involving patients in the benefit-risk assessment of medicines, using a Grounded Theory (GT) approach. The framework which was therefore developed is displayed subsequently.

**A proposed semi-quantitative framework for involving patients in the B-R assessment of medicines, incorporating patient views as key criteria in decision-making**

***Stage 1 - Identification of B-R assessment requiring the patients' perspective***

- A pharmaceutical company selects the drug which requires a B-R assessment. This is likely to be a drug which is undertaking or about to undertake phase III clinical trials, including pivotal trials.

As soon as company procedures are implemented with regards to B-R assessment, a representative would indicate that a 'patients' perspective report' is required.

***Stage 2 - Identification of stakeholders***

- The pharmaceutical company must identify all relevant stakeholders.
- At this point, an independent moderator should be appointed to oversee the process. The independent moderator undertakes a stakeholder assessment, which involves the identification and assessment of patient advocacy group(s) and patient representative(s).
- In addition, the independent moderator identifies hospitals which acted as clinical trial sites for clinical trials of the drug. As part of the Independent identification of stakeholders, investigators involved in undertaking the trials are contacted.
- Patient advocacy group(s) and patient representative(s) confirm their participation in the initiative.
- Hospital investigators confirm their participation in the initiative.

### ***Stage 3 - Benefit-risk stakeholder collaboration meeting***

- The pharmaceutical company invites all relevant stakeholders to a stakeholder collaboration meeting. This is where the pharmaceutical company can present the drug to patient advocate(s) and patient representative(s), provide education and training on the topic of B-R assessment and on the drug's benefit and risk profile. There would also be the opportunity for patient advocacy groups(s) and patient representative(s) to undertake qualitative preference elicitation work, which aids the training but also provides additional information for inclusion within the final analysis and reporting.
  
- The following topics could be included on the agenda:
  - Introductions and overview of initiative and drug to be assessed.
  - Education and training session for patient advocacy group(s) and patient representative(s).
  - Presentation of a comparison of benefit-risk profiles and an analysis of benefit-risk rankings (quantitative).
  - Patient advocacy group(s) and patient representative(s) undertake quantitative B-R rankings with support from statisticians and regulatory personnel.
  - Question and answer session with active patient advocacy group and patient representative participation.

### ***Stage 4 - Patient stakeholder focus groups***

- Investigator involvement is essential. It is proposed that those sites which participated in clinical trials of the drug requiring B-R assessment are invited to participate.

- A simple process of selection would be required which would be monitored by the independent moderator.
- Regulatory (HRA), REC and local R&D approval (in the UK) would be required before a patient stakeholder focus group could be undertaken at site. It is proposed that the investigator and their team are tasked with recruitment and logistics. The independent moderator would then agree a date and time with all stakeholders.
- The day event at each hospital would include a short education and training session, assisted by the patient advocacy group(s) and patient representative(s).
- A qualitative focus group would be undertaken (moderated by the independent moderator).

#### ***Stage 5 - Analysis and reporting***

- The focus group data would be transcribed and thematic analysis would be undertaken. Themes would be identified which would subsequently be presented back to participants for member checking (quality control).
- Once complete, the themes would then be confirmed and documented and a patients' perspective report is generated.
- The reports would be combined with any other patient elicitation data already collected, such as preference elicitation study data. However, the core elements of the report would be:
  - Summary report of the quantitative benefit-risk rankings from the B-R stakeholder collaboration meeting.
  - Qualitative thematic analysis, highlighting themes most important to patients.

### ***Stage 6 – Presentation to regulatory agencies***

- A report would be published and submitted to regulatory agency for consideration during B-R discussions. Patient advocate(s) and patient(s) should be given the opportunity to attend B-R discussion meetings.
- The B-R discussions will be undertaken as per standard process, yet the addition of the patients' perspective report, has the potential to add new information to the assessment, which will benefit regulatory professionals with their decision-making.

## **General discussion**

Each stage of the proposed semi-quantitative framework was developed based on key findings from this research study. In addition to the research findings, several stages of the framework were also informed by discussions with key stakeholders during the conduct of this PhD research programme.

Participants highlighted the need to use both quantitative and qualitative approaches with their patient participation initiatives. However, the methods of data collection for these two different approaches require additional resources. It would be recommended that preference elicitation studies are completed in the first instance, to generate quantitative data which could then be presented to stakeholders. Groups such as the IMI-PROTECT (2018) consortium and PREFER (2018) have already undertaken research into this area.

Stage 1 of the proposed framework would involve the identification of a relevant B-R assessment requiring the patients' perspective. The FDA (2013) highlighted that not all B-R discussions would benefit from patient involvement, however this is perhaps an approach that will change with time. Some decision-making is straightforward, in that the evidence is clear about whether or not a drug should be licenced, for example when data shows a drug is clearly efficacious. A number of participants who completed the surveys highlighted that there are often cases where the decision would be greatly enhanced by the patients' perspective, and it is more likely that borderline cases – examples where decision-making is perhaps not so simple – are probably the most appropriate examples of when the proposed framework could be applied.

Stage 2 of the proposed framework highlighted the need for the identification of all relevant stakeholders – including representatives from industry, patient advocates and appropriately-selected patients. Topic 1 of the semi-structured interviews investigated the methods of involving patients in B-R analysis.

Participants recognised the difficulty in not only identifying and selecting the right patients to be involved, but they also had concerns about the methods utilised to include them. As part of the stakeholder identification, an independent moderator should be employed.

The independent moderator would be pivotal to the entire process, as they would be key to the way in which the proposed framework is employed. As a result, the recruitment of this individual would require careful consideration from all stakeholders. The moderator could potentially alter the direction of benefit-risk discussions due to the way in which they moderate, therefore they would need a specific set of skills and experience. Perhaps individuals without any previous healthcare experience would be the most appropriate to employ, in order to truly ensure independence. They would however need skills in undertaking interviews and focus groups, therefore individuals with a background in market research could be best placed for this role.

The independent moderator would apply transparency to all levels of the process, including the methods used to identify stakeholders. Part of their responsibilities would be to ensure a wide range of patient advocacy group(s) and patient representative(s) are involved. After reviewing the PREFER consortium's website (2018), it can be seen that they have recently taken a similar approach to the methods utilised within this thesis. Their programmes were recently commenced, verifying the research strategy which was implemented within this programme of PhD research. The PREFER consortium also consider stakeholder involvement essential as well as the education and training of patient advocates, patient representatives and patients. The commencement of this initiative is a positive development. Not only does verify the research strategy employed, but it sheds light on the enormity of the challenge at hand.



The only way to ensure an adequate framework for involving patients in B-R assessment is developed is with the engagement of multiple international stakeholders. As a result, this PhD research adds a unique contribution to the topic of patient involvement in benefit-risk assessment, but also to the literature surrounding patient and public involvement more generally.

The involvement of patient advocacy groups and patient representatives has been shown to be valuable not only in benefit-risk considerations, especially from the standpoint of risk tolerability, but it has also aided the decision-making process (Bernabe *et al.*, 2014). Still, this research has discovered examples where patient advocates were perhaps not the most appropriate stakeholder to involve. There were examples identified during this programme of research where patient advocates and patient representatives perhaps no longer put the needs of patients first; where their motivation for participation may have even been self-serving. For the researcher, the term 'expert patient' was a challenge. On one hand, examples were discovered of patient advocates who described themselves as 'expert patients.' They were in fact experts. Experts in their disease, experts in their treatment and an expert in ethics and with a high moral standing. They were clearly committed to ensuring the voice of others patients are heard. In these cases, the term 'expert patient' is appropriate. However, there were also examples where an 'expert patient' had perhaps demonstrated bias or possibly even had ulterior motives. This issue arose multiple times within the data, and it was the perspective of several participants - including those who represent patient advocacy groups - so it does raise the question about the motivations of some individuals. This is a concern.

Corrie and Finch (2015) described how the expert patient can add value to the process, but they rarely highlighted any potential risks of employing expert patients. The information gathered during the conduct of this programme of PhD research regarding 'expert patients' is a unique contribution to the wider topic of patient and public involvement. The literature rarely criticises expert patients and actively promotes their use. Corrie and Finch (2015) also

suggested that the popularity of using expert patients will only increase. This is inevitable, so it is argued that there must be an honest discussion about the issues that may become more prevalent as a result. All stakeholders, including expert patients, may introduce a level of bias. Thus, it is essential that this is recognised by all parties and it is documented, debated and eventually accepted as an inevitable consequence of involving different people within a process.

Stage 3 of the proposed framework described the benefit-risk collaboration meeting. The data collected during all stages of this programme of research highlighted how education and training are essential for the proposed framework to be a success. The NIHR (2013) have demonstrated multiple examples of how PPI initiatives can be improved by not only training patient representatives but also the researchers conducting research. A training and educational element will therefore be necessary, in order for all stakeholders to positively contribute to benefit-risk discussions.

Stage 4 of the proposed framework described the patient stakeholder focus groups. The independent moderator would be responsible for moderating the patient focus groups within this stage of the framework, in collaboration with patient advocacy group(s) and patient representative(s). The patient advocate, who would have already received training during the B-R assessment stakeholder collaboration meeting, would assist the moderator in explaining concepts to patients during the qualitative focus groups. In fact, it would be expected that information is shared between patient advocate and patient in advance of the patient focus group, to help with their training and awareness.

As limited research had already been completed within this area, for example the project undertaken by Bernabe *et al.* (2014), in the research plan it was decided to expand the types of organisations involved, not only focusing on European organisations but also involving several international stakeholders.

Bernabe *et al.* (2014) reported how patient advocacy groups and patient representatives were involved at the EMA. However, there was no distinction between patient advocacy groups, charities or any examples of direct contact with patients. This was verified during the research, when direct telephone contact was made with the lead researcher of the paper. It was confirmed that only patient advocacy groups who were existing members of the EMA's network were involved. It is understood that using pre-existing links are essential to aid new initiatives, however, any aspects where potential bias can be brought into the process must be limited.

Hoos *et al.* (2015) recognised that improved patient involvement has the potential to drive medicines development, as more relevant and impactful patient outcomes will increase efficiency, whilst make the drug lifecycle more productive (Hoos *et al.*, 2015). This research group also identified the barriers to patient participation, many of which were also highlighted within this programme of PhD research. Education and training, communication, perceptions and cultural barriers were all highlighted as important elements to consider (Hoos *et al.*, 2015). All of these elements emerged within this thesis. Although Hoos *et al.* (2015) noted cultural differences as an important point, this was expanded further within this programme of PhD research, offering a unique contribution to this topic. Previously, demographics were not considered when selecting patient advocates and patient representatives.

Furthermore, the data obtained in the surveys suggested that regulatory agencies, pharmaceutical companies and patient advocacy groups were notably staffed by white, educated, middle-class individuals. Is this a true representation of society? It is clearly not. Some specific diseases are more prevalent in ethnic minority groups, therefore, would these groups be engaged in B-R discussions which affect them? Indeed, they must.

Patient identification and selection must be considered to verify that those patients included were drawn from a range of backgrounds. Tokenism is still a challenge which must be addressed. It appears that patient involvement representing all patients, regardless of their age, gender, ethnicity, sexual orientation, and religion, is still not forthcoming. It is essential that this is addressed.

The patient's voice report on patients who had received organ donation highlighted how patients were willing to accept different treatments before and after transplant, as their risk profile changed (FDA, 2016b). These themes were also identified in Focus Group 1 (Renal), completed in December 2014. This acts as validation of the processes used within the focus groups in Phase III of the research as the FDA produced similar data, two years after the completion of Focus Group 1 (Renal).

The objectivity of patients involved in B-R discussions was a theme which arose multiple times during phase I of the research in particular. Yet, the objectivity of other stakeholders was also seen as inadequate. Examples of bias were identified. Moving forward this must be considered by all stakeholders. With regards to the objectivity of patients, evidence was provided for both sides of the argument. Patients can be influenced by other sources such as negative press, therefore adequate training and education is essential.

Issues still remain, and further research must be undertaken before a proposed framework could be accepted by industry and the regulators. The question now is not whether patients should be involved, as this is unequivocal, but how they can be incorporated into a benefit-risk assessment framework. It is argued that patients should not be involved in B-R decision-making at the current time, yet their voice must be heard. There are multiple ways in which this can occur.

Several potential methods have been considered and investigated by the IMI PROTECT consortium (IMI PROTECT, 2015) although a validated method for including patients has not yet been forthcoming. Quantitative benefit-risk preference-elicitation methods include discrete choice experiments, rating scales, threshold technique, standard gamble and conjoint-analysis (Hauber *et al.* 2013; Hiligsmann *et al.*, 2014).

It is anticipated that the proposed framework would be implemented in addition to other projects, such as quantitative preference elicitation studies, which are most effective with large samples of patients. Any proposed semi-quantitative framework requires testing and validation. As some of the stages are theoretical at the point of writing, they would require testing and validation by a pharmaceutical company. It is possible that this could be undertaken as a future research project in collaboration with industry.

When this PhD research was commenced it was proposed that a quantitative benefit-risk preference elicitation was developed as part of this thesis. It was not until the semi-structured interviews when it became apparent that this was not feasible. One participant, responsible for B-R across a multinational pharmaceutical company, commented how the development of such a method within their organisation involved almost twenty members of staff, working on this method alone.

It was therefore accepted that although B-R preference elicitation data should be collected within the bounds of a semi-quantitative framework, it must be undertaken by those individuals with expertise in preference elicitation techniques. It was at this point that the researcher recognised the element of the proposed framework which could be effectively applied and tested was the generation of qualitative focus groups to discuss the concept of benefits and risks.

Still, the process was challenging and the outcomes were not those which were anticipated. A large proportion of the focus groups were spent explaining the concept of B-R assessment to participants. However, participants did understand the concept after a short discussion, and there were no examples where patients were not able to comprehend the discussion. As part of a semi-quantitative framework, this element should be transferred to a point before the focus group, to ensure the time spent in the focus group is focused on the important topics: the patients' perspective, their insight into their condition and how the drug under investigation affected them.

The data collected during Stage 4 would then be transcribed, coded and a thematic analysis would be undertaken. Representatives from industry in collaboration with the patient advocate(s) and patient(s), with oversight from the moderator, would then write up a report, which would then be presented as part of a regulatory submission. The FDA (2013) have already acknowledged the inclusion of the patients' perspective within their assessments, but the lack of an approved method has limited this work to date.

If a universal framework for patient involvement is ever to be adopted, a unique partnership will be required between all relevant stakeholders; who will need to implement a change of culture within their organisations (Smith *et al.*, 2016) In the context of B-R assessment, these methods could be greatly enhanced when combined with a qualitative element, which would be essential in allowing patients the opportunity to communicate what is most important to them.

## **Study limitations**

### *Survey coverage*

It was accepted that study participants were limited to a number of regulatory agencies, pharmaceutical companies and patient advocacy groups. However, as one participant represented the EMA, they had a large remit. The companies that did participate also represented some of the largest from industry.

### *Semi-structured interviews*

Participants who did agree to continue to phase II may have already had a positive bias about involving patients in benefit-risk, therefore a larger sample may indicate that patient involvement is less acceptable than these data suggest.

### *Patient focus group sample size*

It was recognised that the number of participants who attended each patient focus was lower than would normally be deemed accepted. It was planned for Focus Group 1 (Renal) to have two participants, acting as a pilot session. However, the intention was for at least four patients to attend each of Focus Groups 2-4. However, on the morning of the focus groups patients cancelled their attendance. In future, the researcher would ensure at least eight participants have confirmed attendance, meaning that at least four would attend in the event that participants pull out. Yet, on the other hand, Brain and Clarke (2006) confirm that focus groups with less participants do generate richer data, and after analysis it is argued that all four focus groups generated rich data which contributed to the overall aim of this thesis.

It should also be noted that Focus Group 2 (Cancer) had unique challenges. Four patients agreed to participate, yet, as all four were receiving chemotherapy treatment on the unit on the day of the focus group, their availability changed, depending on their current condition and prioritising their treatment (which could be variable depending on adverse events).

This indicates how involving patients with serious disease, offers its own unique challenges, in addition to those already described.

Qualitative research tends to use much smaller sample sizes when compared to quantitative research (Braun and Clarke, 2013). Nevertheless, although the sample size is of less importance, the concept of 'saturation' is paramount. With regards to the study aim, it was concluded that saturation was achieved, as the same concepts emerged throughout all three phases of the research. Yet, within the disease-specific discussions, there was an opportunity to further delve into the differences between patient groups, yet, due to time limitations, this was not possible. Future work could investigate this concept further.

#### *Member checking*

It was proposed that participants be given the opportunity to review the transcript and the emerging themes, to ensure the data was an adequate representation of their opinions. This process, known as 'member checking' is a form of quality control. However, six participants were unable to review their transcripts, therefore this was a limitation. Yet, the remaining participants accepted the transcript and agreed with the themes which were highlighted, therefore it can be assumed that the level of transcription and thematic analysis was adequate, as the majority accepted the findings.

#### **Recommendations and future work**

It is hoped that further collaborations could be generated between industry, patient advocacy groups(s) and patient representative(s), including collaboration with the PREFER consortium. There is potential for implementing education and training initiatives with all stakeholders on patient involvement in B-R. Also, future work should consider expanding the type of stakeholder involvement. Perhaps clinicians, nurses, pharmacists, family members and carers would all contribute greatly to B-R discussions. In addition, paediatrics could also be considered, involving parents and their children in focus group discussions. It is hoped that a future collaboration



project could be implemented, enabling the researcher to fully test and validate the proposed framework. Although challenges remain, further research on this topic presents a genuine opportunity to significantly enhance the current regulatory framework, which ultimately has real potential to benefit patients.

## **Conclusions**

The question was not whether patients should be involved in B-R assessment, as this was unequivocal, but how they could be incorporated into a benefit-risk assessment framework. Based on the findings from this research, it is argued that - at the current time - patients should not be involved in B-R decision-making. However, their voice must be heard. As systems and processes develop their voice will undoubtedly become louder, but there is still much to do before patients are able to become an equal partner in B-R decision-making. Furthermore, it appears that patient involvement representing all patients, regardless of their age, gender, ethnicity, sexual orientation, and religion, is still not forthcoming. This must be considered going forward.

However, involving patients is essential, and there are multiple ways for this to happen. There are already multiple examples of successful PPI initiatives in healthcare (Corrie and Finch, 2015), which could be considered as best practices by the stakeholders involved in benefit-risk decision-making.

The aim of this research was to propose a semi-quantitative framework for involving patients in the benefit-risk assessment of medicines. The framework which was developed offers a unique contribution to the topic of involving patients in B-R assessment. It is hoped that a future collaboration project could be implemented, enabling the framework to be fully tested and validated. This research, accomplished over a similar time period to those projects completed by the regulatory agencies of the US and Europe, has produced a distinctive contribution to information in this area of research,

while also adding to the wider topic of patient and public involvement. The general consensus published by the FDA and EMA was that patients must be incorporated in the clinical trial and subsequent review process. However, the current study has generated findings some of which may well throw doubt on this assumption.

It is essential that patients are given the opportunity to contribute to B-R decision-making, even if it is concluded that they should not be directly involved in the decision-making. As one participant put it, 'we are all patients.' An important consideration when undertaking qualitative research is the concept of reflexivity: how the researcher affects the social construct and ultimately the data which is collected. For the final focus group, the thesis author recognised this important consideration, when faced with a unique situation: moderating a focus group of patients who have the same disease and same drug treatment as the researcher. After experiencing a similar diagnosis and treatment, this was an interesting situation for the thesis author. Yet, in fact, Focus Group 4 was the most successful. By having something in common with participants, including the same insight into the patient's experience, the thesis author was able to fully connect with the participants, resulting in a richer experience for all involved. The researcher recognises the risk of bias with this situation, yet, bias exists everywhere. As another participant highlighted 'where there are humans, there is bias.' It just has to be recognised and avoided as much as possible.

As patients, our insights into our conditions and how treatments affect us, offer unique experiences and information, which could, perhaps, swing the decision pendulum either way during B-R discussions. There could be no contest. For example, in the case of a new drug for psoriatic arthritis, which has the potential to change the life of many patients who receive it, the B-R balance of such a product is clear. On the other hand, there are examples where expensive life-extending drugs, which may have a negligible efficacy, could give a specific sub-group of patients an extra few months of life.

The statistics and the quantitative analysis are essential; however, we need the patients' perspective in these cases, to help us remember that the numbers we are reviewing refer to real people. They are mothers, fathers, sisters, brothers and grandparents. We must remember why this industry exists: to help people live longer, healthier and happier lives. Thus, all people deserve a say in what could ultimately change their life for the better; and give them valuable extra days, weeks or months to spend with the people most important to them.

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# **Appendix I: Evidence of research training**





**National Institute for  
Health Research**

**Biomedical Research Centre  
Guy's & St Thomas' NHS Foundation Trust and King's College  
London**

## *Certificate of Attendance*

***Paul Cross***

*Attended the following course*

***Qualitative Methods: Data Collection***

***Jean Harrington***

***Monday 21<sup>st</sup> October 2013***

Professor Graham Lord  
Professor of Medicine

## **Appendix II: Peer review**

**TO WHOM IT MAY CONCERN**

**Re: Paul Cross**

**PhD RESEARCH PROJECT**

**Developing and validating a semi-quantitative model for the benefit-risk assessment of medicines, incorporating patient views as key criteria in decision making**

Since attending a course I ran on Qualitative Data Collection, for researchers within the domain of the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Trust and King's College London, Paul has been in conversation with me on several occasions concerning the nature of his research study and the most effective, and yet sensitive, manner to design, run and manage the collection of data.

We have discussed various issues and he has, without fail, striven to refine and improve his method. This has included making fine adjustments to very recent drafts, including his initial approach to patients and the written material such as the Patient Information Sheet and Consent Form.

In his quest to ensure that he approaches his fieldwork as well informed as possible I understand that Paul has engaged with colleagues working in various fields including that of PPI; for example, discussing for his purposes, the optimum number of patients for a focus group and the techniques he might use.

Overall, although there are aspects of Paul's research I am not qualified to comment upon, I do consider that he has designed his qualitative research with care and consideration of his participants, whilst maintaining a clear focus on the purpose of his research.

I believe Paul to be a most thoughtful and reflexive researcher, as such I am certain that during his proposed pilot study he will fully engage with any issues that emerge and produce the changes that will enhance the experience for participants whilst producing robust data to move the field forward.



Jean Harrington  
Research Fellow – Social Science  
NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Trust and King's College London  
Division of Health and Social Care Research

# **Appendix III: Conference presentation**

# Developing a model for the benefit-risk assessment of medicines, incorporating patient views as key criteria in decision making

**Paul Cross**

*BRC Quality Assurance Manager, Guy's and St Thomas'*

*PhD Student at Cardiff University (part-time)*

# Background

- Benefit-risk (B-R) assessment is a pivotal stage of the drug approval process and is integral to the activities of regulatory agencies.
- A detailed assessment is completed using all available pre-clinical and clinical data; to ensure the benefits of the product are carefully balanced against the risks.
- Several frameworks / models exist, however no industry standard:
  - Framework – e.g. the Benefit Risk Action Team (BRAT) framework
  - Quantitative model – e.g. multi-criteria decision analysis and B-R value trees
  - Semi-quantitative model – combination of data review and expert opinion
  - Qualitative – detailed discussions / expert opinion of all stakeholders

# Background

- Benefit-risk assessment is about communicating and making sense of large volumes of data from numerous sources
- Its about breaking down and understanding a problem
- There is a need to communicate issues in a transparent, rational and consistent way to aid in decision making



*In this context the decision is whether the drug should be approved/licensed or not*

# Why involve patients?

- Tysabri (natalizumab) approved by FDA in 2004 for treatment of relapsing remitting multiple sclerosis (RRMS)
- 2005: Drug license was suspended because of associated incidence of PML, a rare neurological disorder
- 2006: Reintroduced due to **high patient demand**, but with strict minimisation measures
- 2009: Further cases of PML postmarketing, B-R was reassessed and Tysabri still has approval.
  
- Current research about involving patients
  - US Food and Drug Administration (FDA) first agency to highlight the need to incorporate patients in regulatory B-R assessment
  - European Medicines Agency via the 'PROTECT consortium': B-R methodology and Patient-Public Involvement
  - Utrecht University Medical Centre, The Netherlands: patient representative involvement in benefit-risk assessment tasks of the EMA

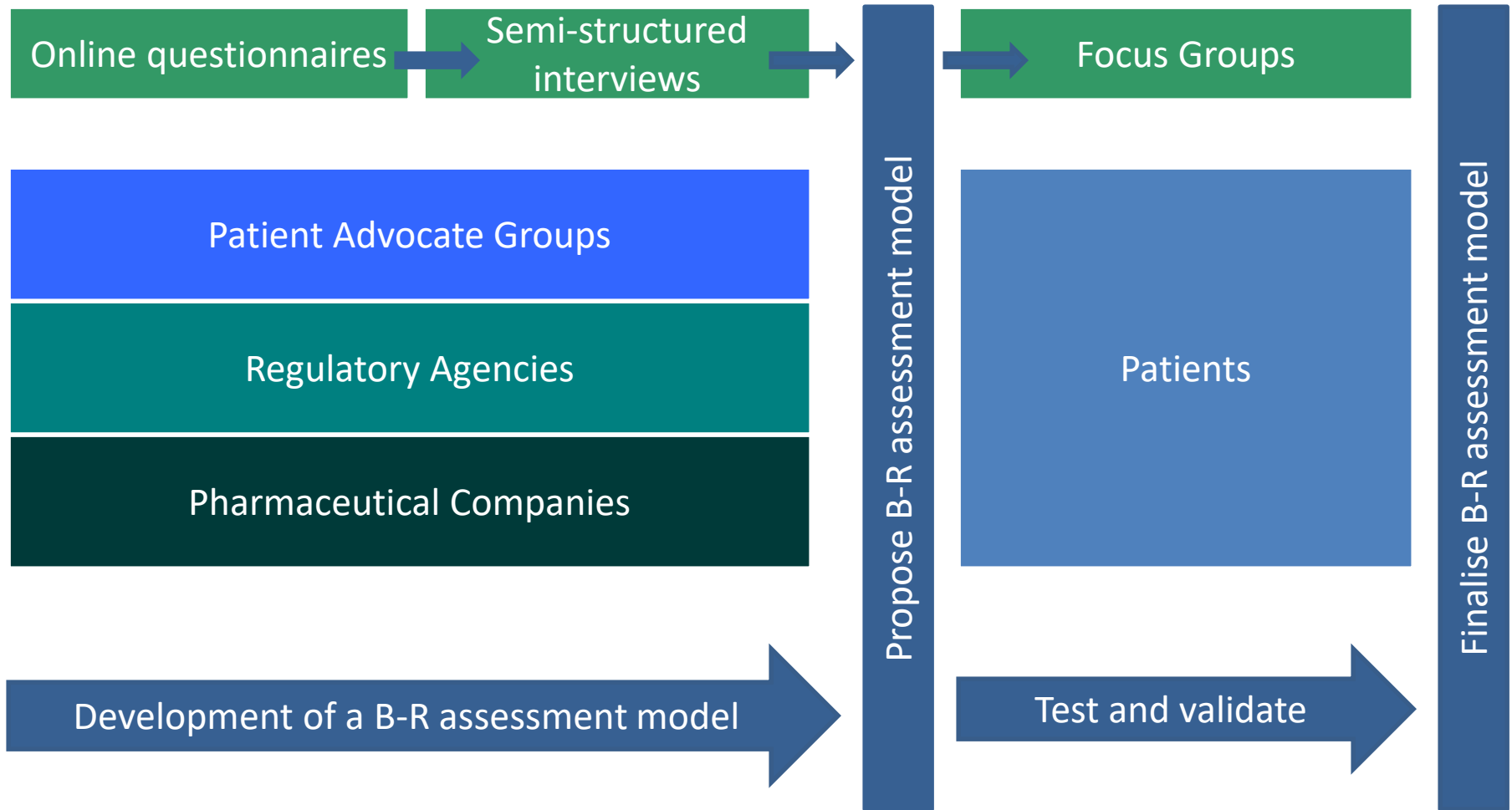


# Aim

- To develop and validate a semi-quantitative model for the benefit-risk assessment of medicines, incorporating patient views as key criteria in decision making

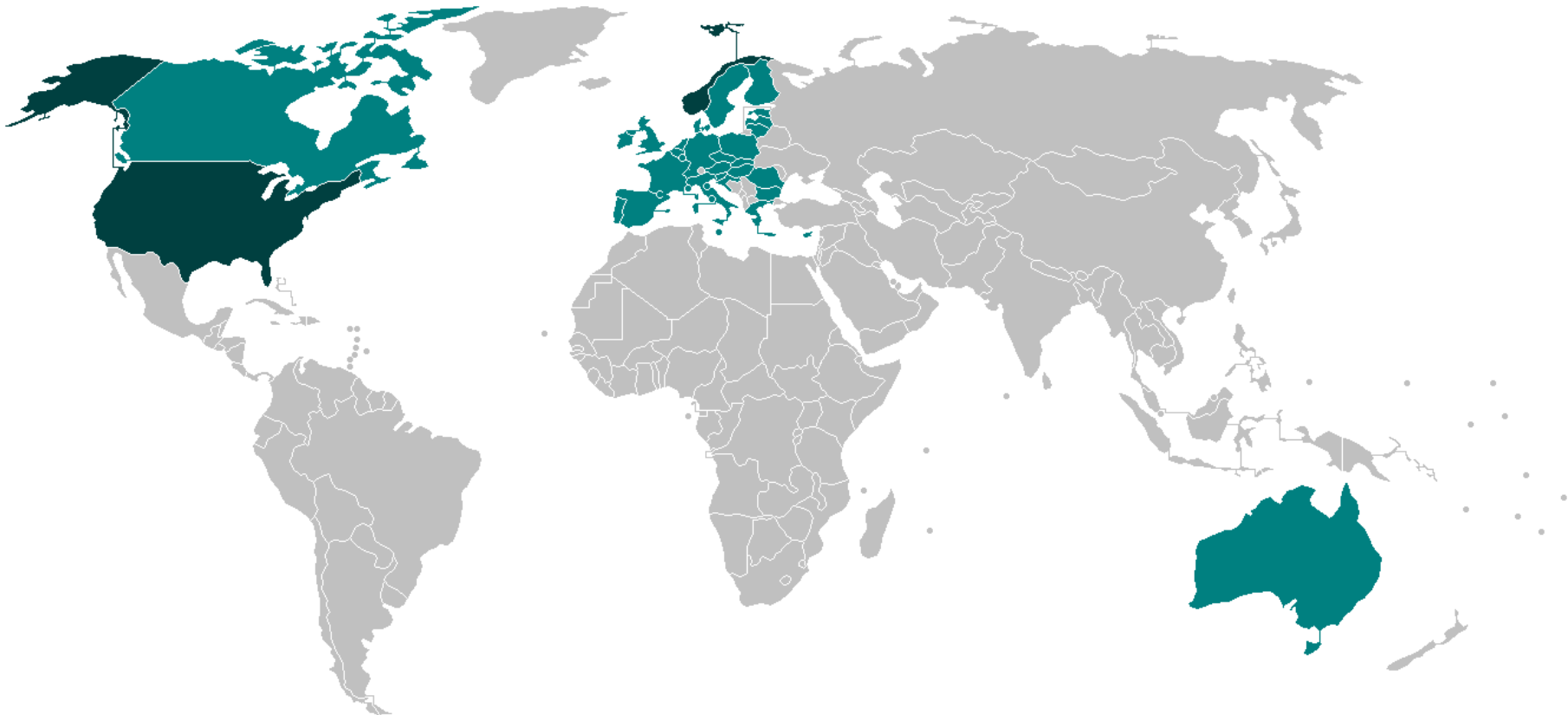


# Study overview / methodology



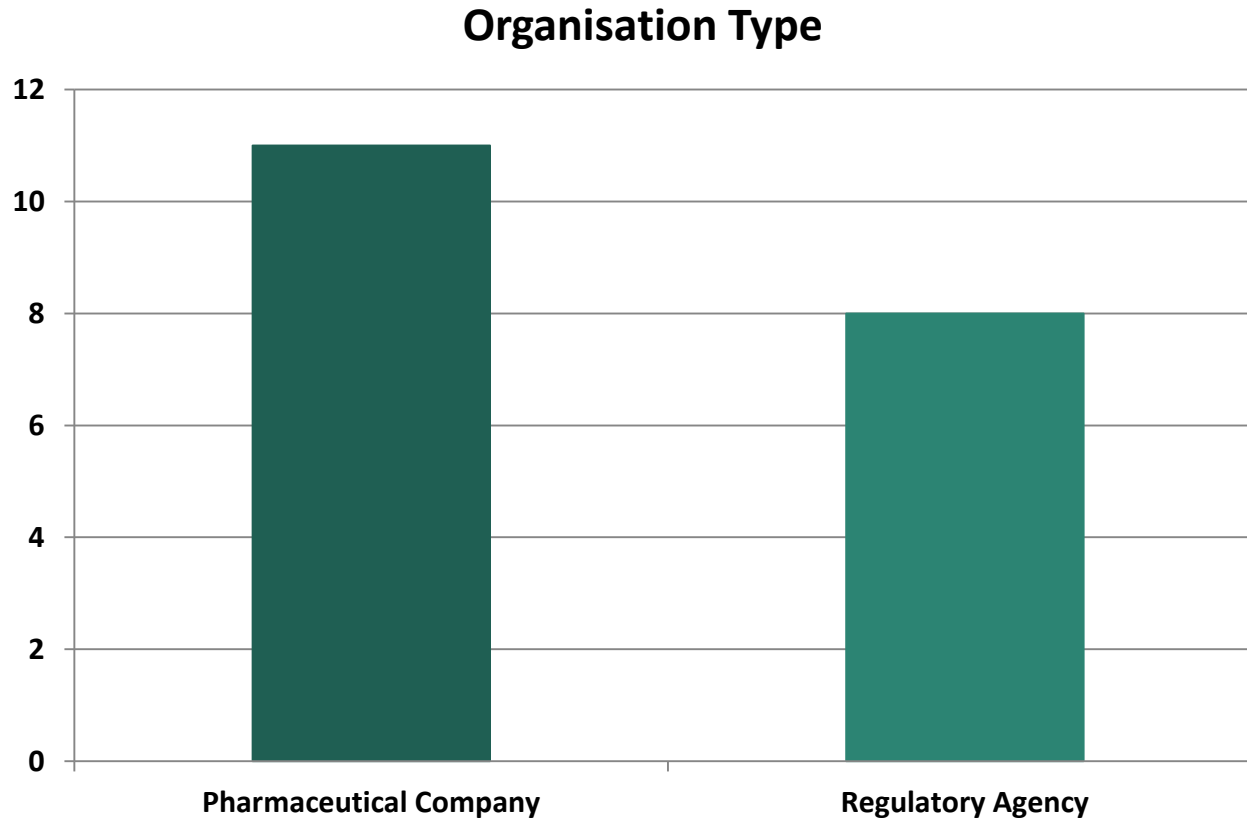
# Questionnaire Recruitment

- **Pharmaceutical Companies** and **Regulatory Agencies**



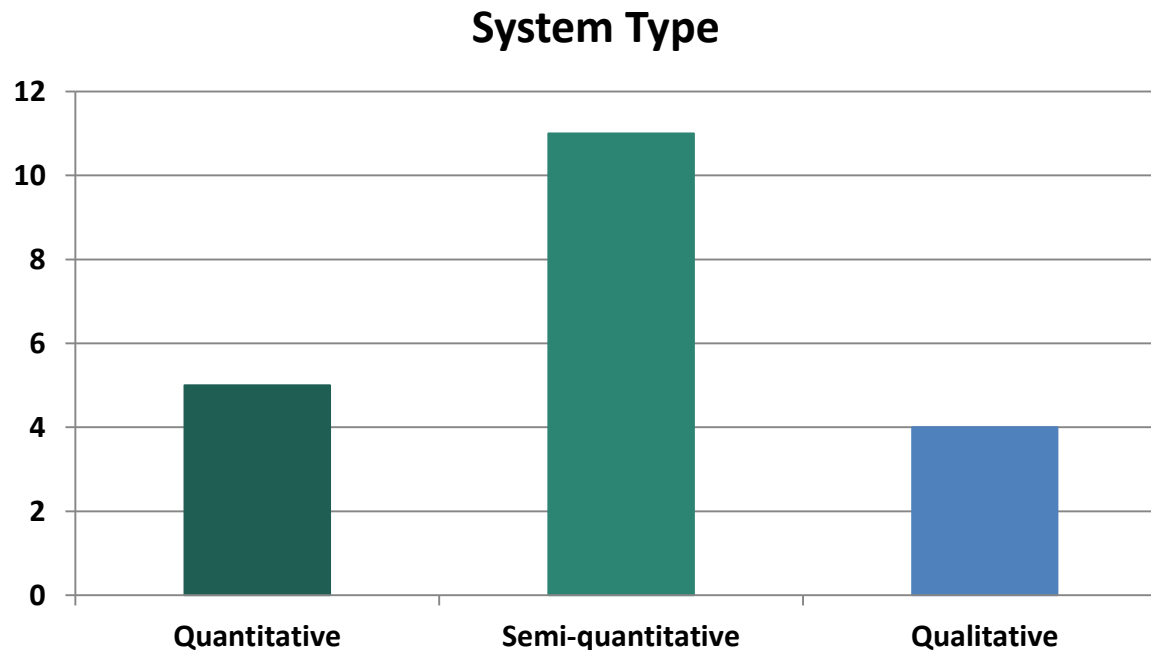
# Questionnaire – Pharma/Regulator

- 19 participants completed to date



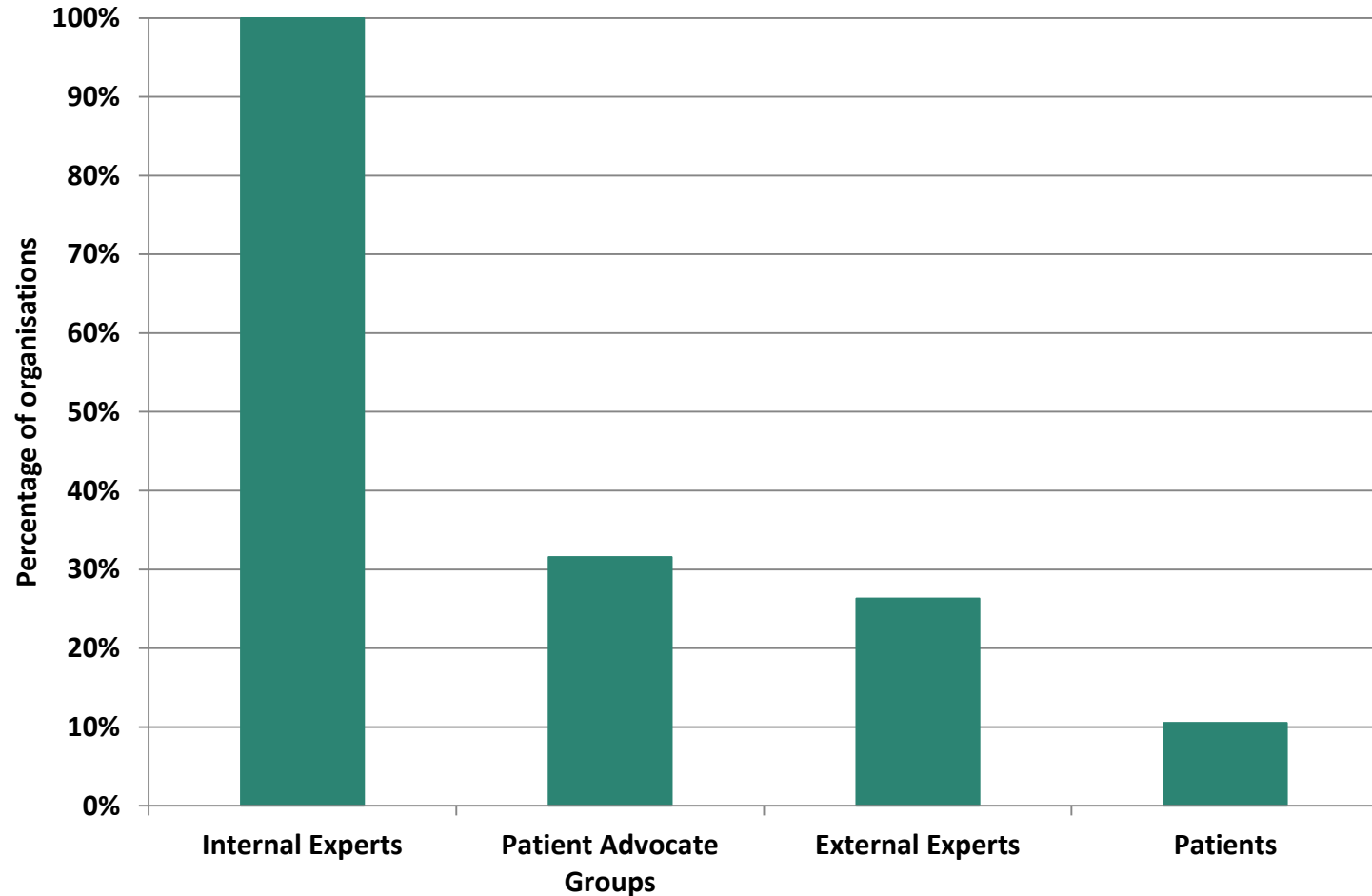
# Questionnaire – Pharma/Regulator

- Which of the following best describes the system used by your organisation for assessing the B-R of a new medicine?



# Questionnaire – Pharma/Regulator

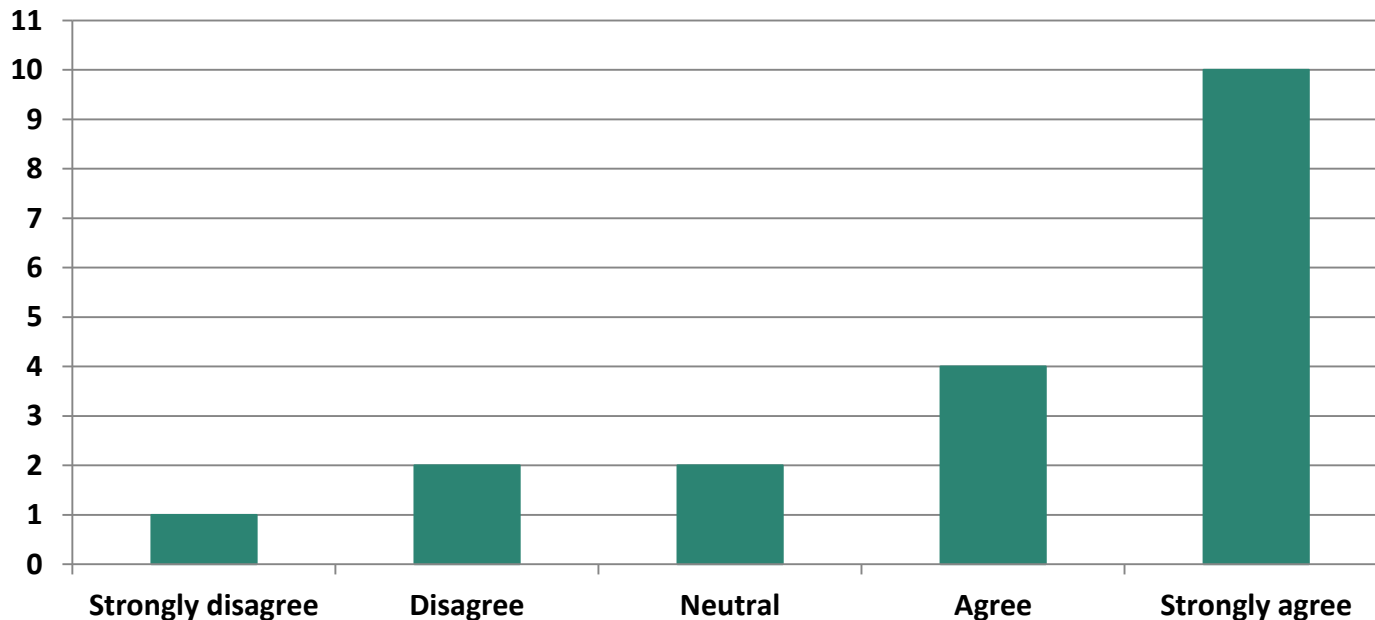
- Who is involved?



# Questionnaire – Pharma/Regulator

- There is a need to incorporate the views of **patient representatives** and/or **patient advocate groups** into **benefit-risk analysis** (i.e. they can answer questions, provide general information on conditions and treatments, state their opinions but no do anything more than this).

Patients in B-R analysis



# Questionnaire – Pharma/Regulator

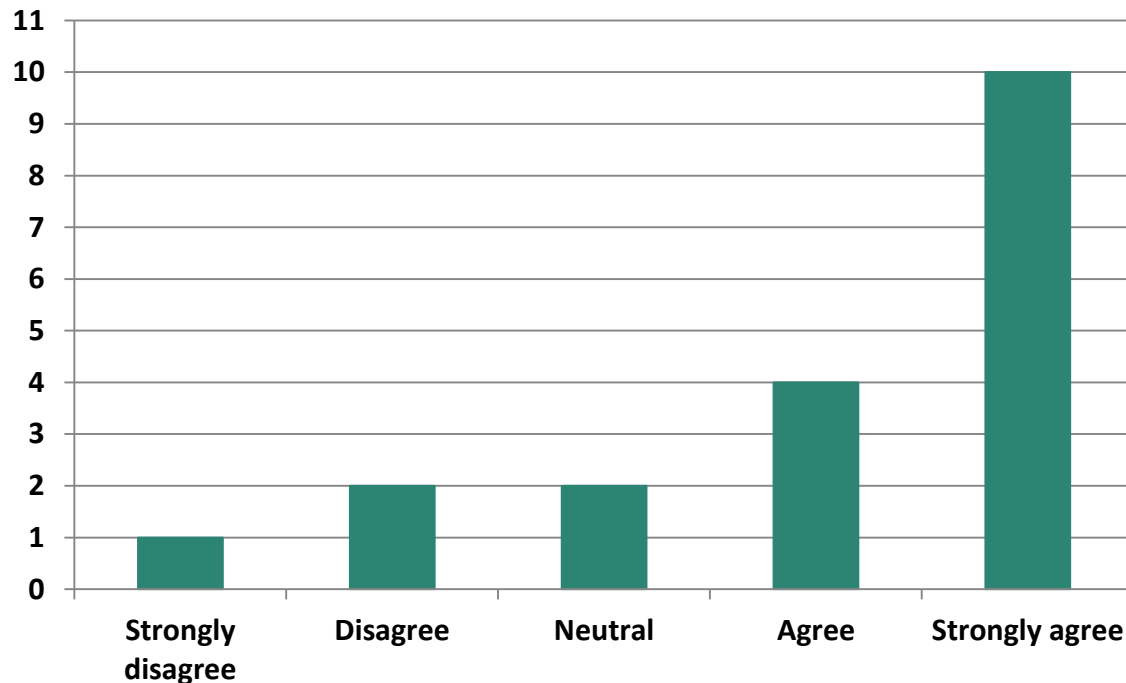
- Reasons for your answer:
- **Disagree:** “Patients are able to provide clear insight into patient reported outcomes and endpoints that can be utilised for this purpose”
- **Neutral:** “If there is no established procedure I would refrain from inclusion of patient representatives”
- **Agree:** “The decision pendulum swings both ways, patients could provide compelling testimony to keep a drug on market which they feel is worth the risk. Quantitatively it may not be”
- **Strongly agree:** “It’s important to understand which endpoints are important to patients” / “Experts cannot provide the needed trade-off between benefits and risks”



# Questionnaire – Pharma/Regulator

- There is a need to incorporate the views of **patients** into **benefit-risk analysis** (i.e. they can answer questions, provide general information on conditions and treatments, state their opinions but no do anything more than this).

Patients in B-R analysis



# Questionnaire – Pharma/Regulator

- Reasons for your answer:
- **Disagree:** “Information from patients could be taken into account but the analysis should be made by specialists and be data driven”
- **Neutral:** “It is difficult to provide complex information, in ways that can be properly understood”
- **Agree:** “Depending on their conditions, e.g. cognitive issues, terminal state etc.), patients may be unable to exercise their rights, hence their caregivers should always be able to stand in for them”
- **Strongly agree:** “Patients’ subjective views on benefit-risk tradeoffs are a prerequisite to making a decision that is for their best interests”

# Questionnaire – Pharma/Regulator

- What do you perceive are the **barriers** to involving patients in the benefit-risk assessment process? Please provide reasons for your answer.

“Methodology of obtaining patient views”

“Structural and logistical challenges in doing something new in the pharmaceutical company.”

“Lack of internal expertise in preference elicitation methods and application. Acceptance of preference elicitation by regulators.”

“Lack of established best practice on how to do this”

“Some countries would have to deal with pre-existing structures such as insurance companies who might be resistant to a bigger involvement of patients making decisions”

“Identification of correct patients that are able to give input”

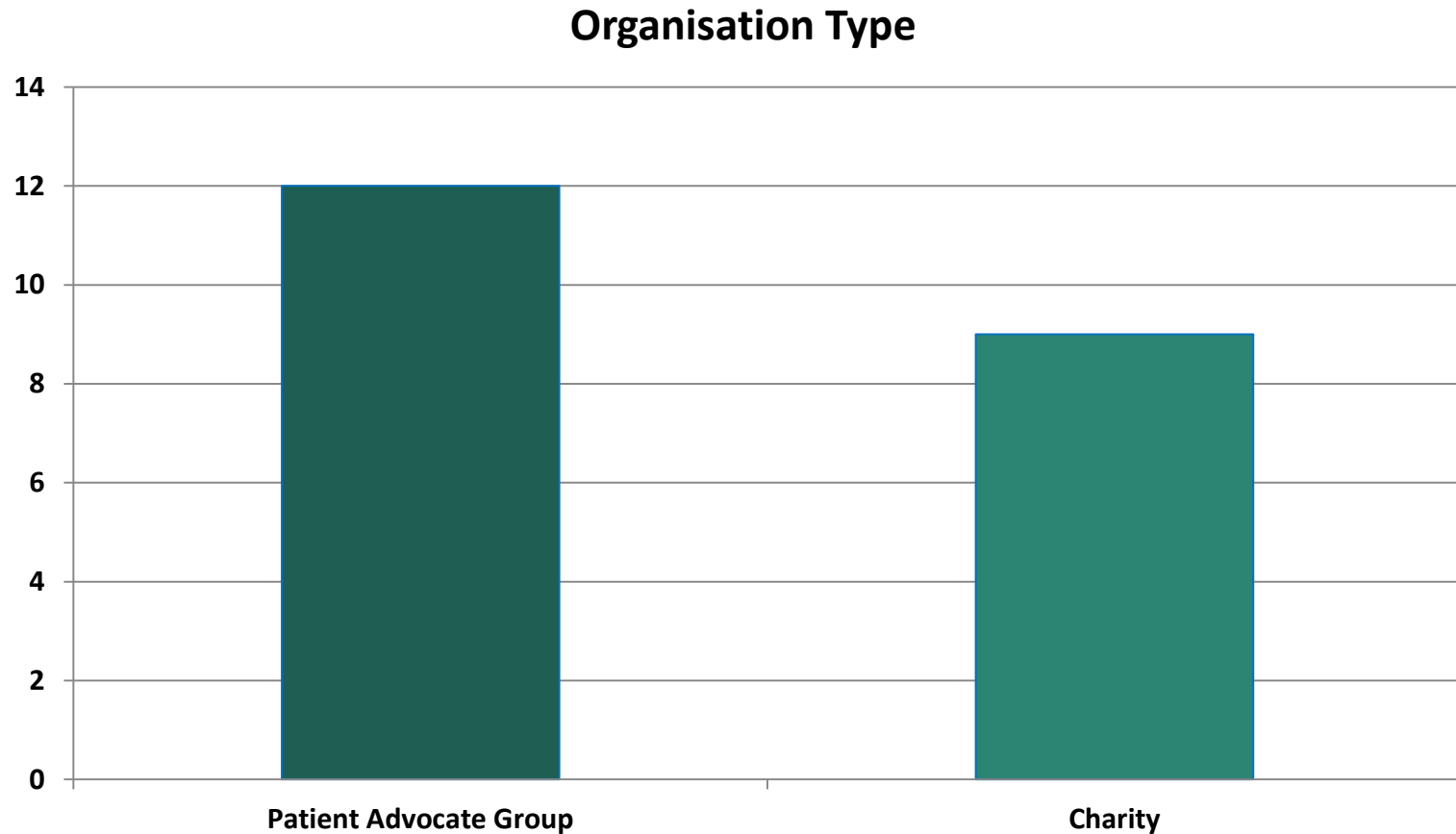
# Questionnaire Recruitment

- Patient Advocate Groups



# Questionnaire – Patient Advocates

- 20 participants completed to date



# Questionnaire – Patient Advocates

- Do you feel there is a need to incorporate patient views into the benefit-risk assessment of medicines? Please provide reasons for your answer.

“Of course, often the side effects are not taken in consideration and for the patient the quality of life is very important”

“Yes. Patients are often more willing to tolerate risks that non-patients would not.”

“Its important to understand what risks patients see as being important to them. What you may see as a minor risk may be crucial to patients.”

# Questionnaire – Patient Advocates

- What is your personal opinion on the perceived **risks/negatives** of incorporating patient views in benefit-risk assessment?

“There is a possibility that patients could accept medicines with lower level of benefits due to absence of alternatives”

“While many individuals can well represent their own views and experiences, unless they have contact with others living with the same condition/disability they may not be able to represent a wider experience”

“Some patient views will be very personal and subjective – their experience may outweigh a perception of possible benefits to others from a treatment if theirs was inappropriately delivered and their experience was poor”

# Questionnaire - limitations



- Still awaiting completion of some questionnaires, response or non-response bias?
- Have not yet reached **saturation** – further data to collect and analysis still to undertake



# Next steps

- Semi-structured interviews with pharma, regulators and patient advocates
- Patient Focus Groups
  - Oncology
  - Rheumatology
  - Cardiovascular
  - Allergy
  - Renal (*1 pilot focus group already completed*)
  - HIV





## Summary



- In general, a cross-section of pharmaceutical companies and regulators who participated were generally supportive of involving patients in B-R assessment.
- Patient advocates are supportive of becoming more aware of and involved in B-R assessment initiatives.
- However, a number of logistical and procedural challenges remain, which must be addressed before this can be realised.

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***Thank you for listening***

***Any questions?***

## **Appendix IV: Conference poster**

**Introduction / Aim**

•Before new medicines are approved for marketing, safety, quality and efficacy must be assessed. A detailed assessment is completed using all available data; to ensure the **benefits** of the product are carefully balanced against the **risks**.

•**Benefit-risk (B-R) assessment** is a vital stage of the drug approval process.

•Involving patients in B-R assessment is a recent innovation. Patients may view benefits and risks very differently when compared with the views of pharmaceutical companies or regulatory assessors. However, there has been limited research in this area.

•The aim of this research is to develop and validate a method to include patients in this process.

**Methodology**

•**Scoping exercise** - Questionnaires were submitted to (1) - pharmaceutical companies, E.U. and G20 country regulatory agencies and (2) - patient advocacy groups and charities across Europe, using SurveyMonkey, to obtain their opinions on involving patients in B-R assessment.

•Data was collected on country (Fig. 1), type of organisation (pharmaceutical company or regulator, Fig. 2) and the type of benefit-risk assessment model / system used (qualitative, semi-quantitative or quantitative; Fig. 3), need for patient involvement (Fig. 4) and who is currently involved (Fig. 5).

•Data is currently informing the development of a semi-quantitative model for including patients in B-R assessment.

•This involves thematic analysis of qualitative focus group data in combination with quantitative ranking of benefits and risks.

**Results**

**Questionnaire to Pharmaceutical companies and Regulatory Agencies**



Figure 1 – Global distribution of responders

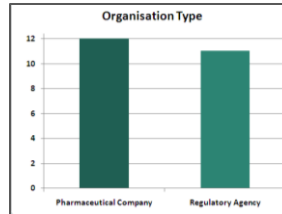


Figure 2 – Organisation Type

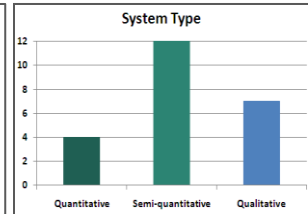


Figure 3 – The majority of responders use a semi-quantitative approach

**Questionnaire to Pharmaceutical companies and Regulatory Agencies: Responses**

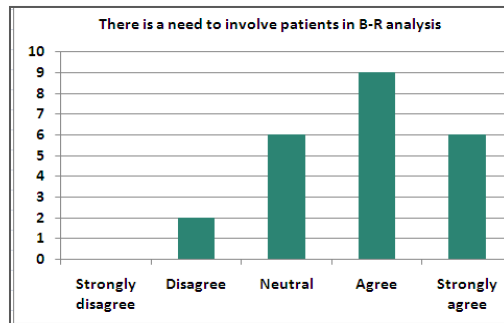
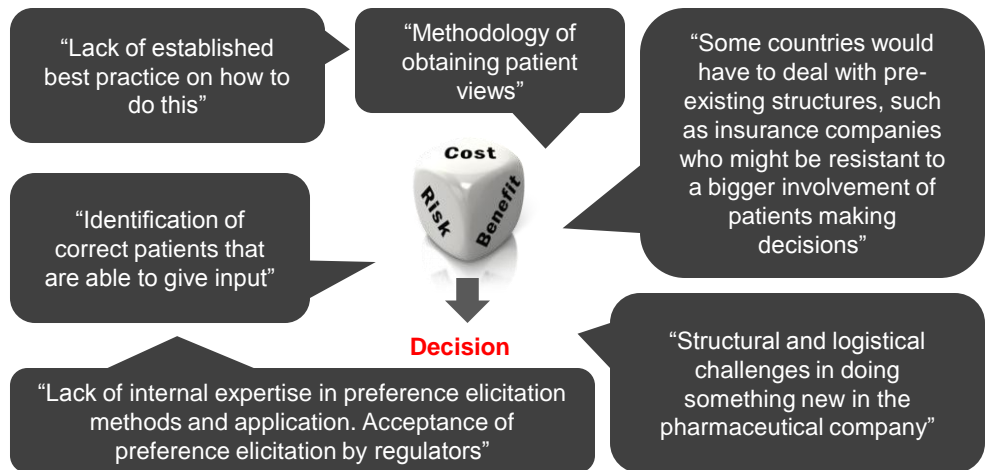


Figure 4 – The majority of responses agreed that patients should be involved



Figure 5 – Only 9% of responders involve patients at the current time

**Question: What are the barriers to involving patients?**



**Conclusions**

•Considering most participants agreed or strongly agreed that patients should be involved, only 9% responded that patients were currently incorporated in the B-R assessment process at their organisation.

•Challenges included a deficiency of established best practice and a lack of validated methods. Patient identification and selection were also key challenges and in addition, how the selected group could be representative.

•Patient Advocacy groups were very supportive of further patient involvement. Qualitative focus groups are currently underway with patients at Guy's and St Thomas' Hospitals in London, UK. Therefore further research needs to be completed and the project is ongoing.

# **Appendix V: Research protocol**



**PhD RESEARCH PROJECT  
STUDY PROTOCOL**

**Developing and validating a semi-quantitative model for the benefit-risk assessment  
of medicines, incorporating patient views as key criteria in decision making**

**Protocol Version:** Version 2.0

**Date:** 22<sup>nd</sup> September 2014

**Sponsor**

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**Statement**

The Chief Investigator, Principal Investigator, Sponsor and representatives from the participating site have discussed this protocol. The Chief Investigator and Investigator Site Staff agree to adhere to this protocol at all times.

**Professor Robert Sewell**

Chief Investigator

Date: 22/09/2014

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## 2. Background

Before a new medicine is approved for marketing, data must be available to demonstrate the safety and efficacy of the medicinal product. A detailed assessment is completed using all available pre-clinical and clinical data; to ensure the benefits of the product are carefully balanced against the risks. Benefit-risk assessment is a pivotal stage of the drug approval process and is integral to the activities of regulatory agencies (ICH, 2012). 'The assessment of the benefit-risk in the context of a new drug application is a central element of the scientific assessment of a marketing authorisation' (EMA, 2007).

There are a number of different models and frameworks used by pharmaceutical companies and regulators for benefit-risk analysis. For example, the multi criteria decision analysis (MCDA) model 'uses an algorithm that combines value judgements along multiple dimensions' (EMA, 2007). 'Decision analysis' is widely used throughout the world of business as well as within various government departments. The MCDA model involves developing a list of relevant benefit and risk criteria that can then be used for determining a benefit-risk profile. These criteria are then organised depending on their importance in the overall decision (termed 'weighting'). Each criterion can be scored, weighted and then a calculation can be undertaken using computer software (EMA, 2007).

In their book, 'Benefit-Risk Appraisal of Medicines, A systematic approach to decision-making' published in 2009, Mussen, Salek and Walker presented a detailed case for the reasons why a standardised model for benefit-risk assessment of medicines is required. Previously there was no standardised model for such an assessment and therefore regulatory agencies and industry conducted the benefit-risk assessment process using a variety of models (Mussen, Salek and Walker, 2007a, 2007b). By developing a standardised model it was hoped that a more reproducible system could be implemented, which may one day become the industry standard. This quantitative model, based around multi-criteria decision analysis, was devised and validated by the authors.

Regulators agree that there is a great deal of work to be done with regards to standardising benefit-risk analysis. The United States Food and Drug Administration (FDA) are also working on this issue and are in fact leading the way at the current time. In their recent publication 'Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making' (FDA, 2013) they write their case for a complete review of their current systems and processes. The authors state that 'in the past, some FDA stakeholders have indicated that there is room for improvement in the clarity and transparency of FDA's benefit-risk assessment in human drug review' (FDA, 2013).

Although the FDA publish documentation related to their decision-making online, they also point out that 'while FDA takes great care to clearly explain the reasoning behind a regulatory decision in these documents, the clinical analysis may not always be readily understood by a broad audience who may wish to understand FDA's thinking' (FDA, 2013).

The stakeholders involved in benefit-risk analysis include pharmaceutical companies, regulatory agencies as well as healthcare professionals such as prescribers (Mussen, Salek and Walker, 2009). One key area that is addressed by Mussen, Salek and Walker (2009) is the different perspectives of professionals involved in benefit-risk analysis. Different stakeholders have both different perspectives and different priorities depending on the nature of their work. 'Since benefit-risk assessment is essentially a value judgement, it will inevitably be prone to a number of biases' (Mussen, Salek and Walker, 2009). These biases are informed by the nature of the work of the individual making the assessment. In addition, different individuals may give different views at different times, even when presented with the same data; which demonstrates the subjective nature of the assessment process (Mussen, Salek and Walker, 2009).

The primary objective of pharmaceutical companies is to demonstrate sufficient efficacy of a product to receive regulatory approval (Mussen, Salek and Walker, 2009). In addition, the company would hope that healthcare professionals prescribe the medicine (Mussen,

Salek and Walker, 2009). A pharmaceutical company may accept a risk depending on how likely that risk will affect the chance of the product receiving a licence. They also consider the possibility of legal liability in the event of serious adverse events (Mussen, Salek and Walker, 2009). 'Regulatory agencies view the benefits and risks for the nation as a whole rather than for individuals' (Spilker, 1994; Cromie, 1997). They require evidence for an established and favourable safety profile. They will also consider the cost of a treatment by comparing it to treatment alternatives; as the pharmacoeconomics of medicines also influence their decision-making. Regulators 'usually focus on risks more than benefits due to their responsibility for ensuring public health' (Mussen, Salek and Walker, 2009).

In general, 'regulators tend to view patients as incompetent to judge risks and benefits,' (Mussen, Salek and Walker, 2009). However, this is unfounded and opinions are changing. Patient-Public Involvement (PPI) has become increasingly important in recent years. As patients become more informed, due to increased access to information such as via the internet, their well-informed opinions are increasingly important. The National Institute of Health Research (NIHR) explain that PPI 'can lead to better research that is more focussed on the needs of patients and can accelerate the transfer of research evidence into practice' (NIHR, 2013). Patients and the public can participate in research in a number of ways. Most often, their participation involves working with researchers, clinicians, research managers and health economists.

Involving patients in the research process is not a new concept; however involving patients in the area of benefit-risk analysis is relatively new. It has been identified by several parties that patients have a vital role to play as they can offer a different and unique point of view. This is because patients, who are taking medications for their various conditions, may view benefits and risks very differently when compared against the views of pharmaceutical companies or regulatory assessors. Patients tend to 'view benefits in terms of how their symptoms improve, by how much and for how long' (Mussen, Salek and Walker, 2009). Patients view risks with respect to their chance of having an adverse reaction or a lack of effect resulting in a relapse of their underlying disease (Mussen, Salek and Walker, 2009). It is important to note that patients may sometimes 'focus excessively on any risks to

which their attention is drawn' (Mussen, Salek and Walker, 2009). The patients' 'perception of risk may therefore be different from actual risk' (Mussen, Salek and Walker, 2009). However, patients' opinions are 'often very personal, subjective value judgements that can only be based on religious, philosophical, and social values' (Veatch, 1993). It is therefore essential that a patient is given all the information and not only information on the benefits or side-effects, so that they can make an unbiased decision.

Many factors influence how a patient views the benefit and risks of a particular treatment. They are 'influenced by the media, by healthcare professionals and by friends and family' (Mussen, Salek and Walker, 2009). This makes for a very complex picture, which can be unique to every individual. In addition, the way in which a patient makes their assessment is strongly influenced by the way in which the data is presented. For example, if side effects have been emphasised by a healthcare professional, when in fact the risk is low, the patient may still be influenced negatively.

It is clear from recent developments that patient-focused drug development is going to continue to gain in popularity and will be used more widely. The FDA's project aim's to address how to use the patient's perspective to inform their decision making but to also include their views in a benefit-risk assessment process. Mullard (2013) states that once patient opinions have been collected, using a variety of means (from meetings or from surveys), 'the next challenge becomes turning anecdotal reports into structured and meaningfully [*sic*] data that can be incorporated into an assessment framework' (Mullard, 2013; FDA, 2013b). Involving patients in regulatory decision-making could greatly improve and enhance the benefit-risk assessment process. Leong et al (2013) demonstrates that there is need for a universal benefit-risk assessment framework which incorporates a variety of different tools and methods, which could be the industry and regulatory standard.

Leong (2013) also highlights the need to incorporate patients into any agreed process. It is on this basis that this research project will investigate how qualitative data obtained

directly from patients themselves can be incorporated into a benefit-risk assessment model. The model developed during this study will need to be tested and validated.

### **3. Aim**

To develop and validate a semi-quantitative model for the benefit-risk assessment of medicines, to incorporate patient views as key criteria in decision-making.

### **4. Objectives**

- Complete a literature review on the current models of benefit-risk assessment of medicines, focusing on the inclusion of patient views as key criteria.
- Identify the current models/processes used by regulators to incorporate patient views into benefit-risk analysis (US, EU, UK).
- Undertake patient focus groups to collect information directly from patients and analyse this data using NVivo to identify the key themes and issues.
- Propose a method to incorporate this qualitative data into a model or framework for the benefit-risk assessment of medicines.
- Test and validate the method.
- Obtain further information from regulators, pharmaceutical companies and patient expert groups by collecting data via questionnaire.

## 5. Methodology - Qualitative Study - Patient Focus Groups

### *Recruitment*

The study would be introduced to patients during their routine clinical appointments by doctors or nurses responsible for their care. The doctor or nurse will gain approval from the patient to be contacted. The researcher will send an invitation letter and Patient Information Sheet with a tear off slip (and prepaid stamped addressed envelope) to send back to the researcher, indicating whether they would like to participate or not. Patients will be given about ten days to think about participating before the researcher contacts them to confirm that they are happy to continue (except for those patients who have already informed the researcher that they do not wish to participate). Once the patient is happy to participate, the researcher will book the participant in to attend an appropriate patient focus group (depending on the condition that they have).

### *Patient Focus Groups*

Initially, a pilot group will be developed which will help to determine how the patient focus groups will be run and also to gain insight into how this type of meeting will progress. In addition, work will be undertaken to determine the optimum number of participants in each group. Patient focus groups will be formed in several different indications including:

- Cancer
- Rheumatology
- Cardiovascular
- Inflammatory and Immune System
- Renal and Urogenital

### *Patient Focus Group Logistics*

The researcher will arrange for a taxi if the patient requests it, otherwise patients will visit the hospital at an arranged time. The patient focus group will consist of up to five people at a time. Refreshments will be served during the meeting.

### *Consent*



All patients will be asked to sign a consent form before the start of the patient focus group and the researcher will check that all patients are happy to continue and for their conversation to be recorded.

#### *Demographics Questionnaire*

Patients will be asked to complete a demographics questionnaire which may help the researcher in the subsequent data analysis.

#### *Group Discussion*

A list of prompts will be used by the researcher which will be followed when asking questions. By following the same standard it can be ensured that the conversation follows a similar agenda for each meeting, however the make-up of each group will be inherently unique, which is an important element in this type of qualitative study.

#### *Follow-up*

Patients may be contacted by telephone during the data analysis phase to confirm some aspects of their views/opinions if this becomes necessary.

## **6. Selection of Subjects**

#### Inclusion Criteria

- Male and female patients
- Aged at least 18 years old
- Prescribed medications and taking medicines for their conditions or patients who have previously taken medications for their conditions.

#### Exclusion Criteria

- Patients not willing to be recorded as part of a patient focus group meeting.

## **7. Data Collection**

The Trust has strict confidentiality policies which the researcher will adhere to at all times. The patient focus groups will be recorded and therefore it may be possible to identify patients from such recordings. All recordings will therefore be stored in a locked cabinet in a secure office. This data will be anonymised at the point of transcription to ensure confidentiality is maintained. Study data will be stored in a the Study Master File located in the Clinical Research Facilities at Guy's and St Thomas' NHS Foundation Trust for a minimum of fifteen years after the study is completed, in line with Cardiff University's Data Retention Policy.

## **8. Data Analysis**

The qualitative data collected from the patient focus groups will be analysed using the 'NVivo' software. This software will assist the researcher in interrogating the data, identifying both common themes and more subtle connections. A method will be developed after the focus group meeting stage of the study to incorporate this data into a benefit-risk assessment model or framework.

## **9. Statistics**

As this is a qualitative study, the sample size will be dependent on the point at which saturation occurs. There will be several patient focus groups of different indications included in this research study.

## **10. Informed Consent, Patient Confidentiality and Ethical Implications**

Patients may need to divulge sensitive, embarrassing or upsetting information to the researcher during the focus group meeting. Patients will be informed at the start of the meeting that they only need to provide as much information as they feel comfortable with. If they do not wish to answer a question, or discuss a topic any further, they are free to say so at any time. The researcher will ensure patients feel comfortable to continue by regularly checking on all individuals in the group. In the event that a patient becomes

distressed, they can discontinue at any time. Patients will be directed to the Guy's and St Thomas' NHS Foundation Trust Patient Advice and Liaison Service (PALS) in the event that they need further advice or guidance.

Informed consent will be taken before commencing the patient focus group. However, the rights of patients will be respected at all times and it will be made clear to patients that their participation is voluntary and that they are free to withdraw at any time, without giving a reason and without their medical care or legal rights being affected.

Data will be anonymised at the point of transcription to ensure patient confidentiality is maintained at all times. Although there will be no direct benefit to those patients that are included, it is hoped that the findings from this study may help improve current processes and procedures, which may improve the care of patients in future.

## **11. Research Study – second phase**

The second phase of this research will involve the development of a questionnaire which will be sent to patient advocate groups, regulators and pharmaceutical companies. This aspect of the research will be reviewed and approved by the Cardiff University Ethics Committee before it commences.

## **12. Quality Assurance**

The study may be selected for monitoring or audit by the research Sponsor, Cardiff University or by the host organisation, Guy's and St Thomas' NHS Foundation Trust, in line with their research governance monitoring processes.

## **13. Research Governance**

### **Research Ethics Committee (REC) and Research & Development (R&D) Approval**

The study will be reviewed and approved by an appropriate REC and by the R&D department at Guy's and St Thomas' NHS Foundation Trust.

## **The Research Governance Framework for Health and Social Care**

The study will be carried out in accordance with the NHS Research Governance Framework for Health and Social Care 2005.

### **Insurance**

The Sponsor, Cardiff University, will provide trial Insurance and Indemnity.

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# **Appendix VI: Semi-structured interview schedule**

**Study Title: Developing a model to assess the benefits and risks of new medicines to incorporate patients' views**

Semi-Structured Interview Schedule

Version 1.0 dated 10<sup>th</sup> June 2015

**1. Welcome**

- What is this research about?
- What will I do with the information collected?

**2. Consent**

**3. Demographics Questionnaire**

- Why do I need to collect this information?

**4. Introductions**

**5. Interview Topics**

**Topic 1 – Benefit-risk (B-R) Assessment**

- Methods to include patients.
- What are the benefits of including patients?
- What are the challenges/negatives of including patients?

**Topic 2 – Education**

- Should a patient's level of education influence if they should be involved in B-R analysis?

**Topic 3 – Is there potential for bias?**

- Could patient involvement bias regulatory decisions?



# **Appendix VII: Focus group schedule**

# **Study Title: Developing a model to assess the benefits and risks of new medicines to incorporate patients' views**

Patient Focus Group Schedule

Version 1.0 dated 14<sup>th</sup> July 2014

## **1. Welcome**

- What is this research about?
- What will I do with the information collected?

## **2. What is a focus group?**

- All views welcome to gather a diverse set of information.
- We expect views to be different.

## **3. Consent**

## **4. Demographics Questionnaire**

- Why do I need to collect this information?

## **5. Rules**

- All members should be given the opportunity to give their views.
- The meeting will be recorded, but this will be kept confidential.

## **6. Introductions**

## **7. Focus Group Topics**

### **Topic 1 - Disease overview**

- Which symptoms have the most significant impact on your daily life?
- Depending on what is raised, ask about particular symptoms in detail.
- How do these symptoms impact on your daily life?
- Are there specific activities that are important to you but that you cannot do because of these signs or symptoms?
- How have your signs or symptoms changed over time?

## **Topic 2 - Patient Perspectives on Current Approaches to Treating**

- What are you currently doing to help treat the condition or its signs/symptoms?
- How well does this current treatment regimen treat these symptoms?

## **Topic 3 – Scenario for Discussion**

- Imagine that you had the opportunity to consider participating in a clinical trial for an experimental therapy. What are your views on taking a new medicine?

## **Topic 4 – Benefit / Risk Assessment**

- Discussion on the different ways that patient views could be incorporated.
- How would you like this to happen e.g. visual (graphs, images)?

## References

Food and Drug Administration. (2013b). Patient-focused drug development: Disease Area Meetings Planned for Fiscal Years 2013-2015. Available at: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm> last accessed, 20th November 2013.

# **Appendix VIII: Research approvals**

<b>Cardiff School of Pharmacy and Pharmaceutical Sciences, Research Ethics Approval</b>
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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 the following study:

Project title:	Developing and validating a semi-quantitative model for the benefit-risk assessment of medicines, incorporating patient views as key criteria in decision making
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This is a/an:	Undergraduate project	
	ERASMUS project	
	Postgraduate project	X
	Staff project	

Name of researcher: (PG/Staff projects only)	Paul Cross
Name of supervisor(s):	Prof R Sewell

<b>STATEMENT OF ETHICS APPROVAL</b>
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**This project has been considered and has been approved by the Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee**

Signed  Name R Price-Davies Date 18/2/15  
(Chair, School Research Ethics Committee)



## Health Research Authority

### NRES Committee South East Coast - Surrey

Bristol Research Ethics Committee Centre  
Whitefriars  
Level 3, Block B  
Lewins Mead  
Bristol  
BS1 2NT

Telephone: 0117 342 1380

30 September 2014

Professor Robert Sewell  
Professor of Pharmacology and Director of Dip Clinical Research  
Cardiff University  
Redwood Building  
King Edward VII Avenue  
Cardiff, Wales  
CF10 3NB

Dear Professor Sewell

<b>Study title:</b>	<b>Developing and validating a semi-quantitative model for the benefit-risk assessment of medicines, incorporating patient views as key criteria in decision making</b>
<b>REC reference:</b>	<b>14/LO/1589</b>
<b>Protocol number:</b>	<b>N/A</b>
<b>IRAS project ID:</b>	<b>143944</b>

Thank you for your letter of 08 September 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Gemma Oakes, [nrescommittee.secoast-surrey@nhs.net](mailto:nrescommittee.secoast-surrey@nhs.net).

### Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

## Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

## Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett ([catherineblewett@nhs.net](mailto:catherineblewett@nhs.net)), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

## Ethical review of research sites

### NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

## Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper	1	08 August 2014
Covering letter on headed paper [Covering Letter ]	1	22 September 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Certificate Number: Y016458QBE0114/165]		01 August 2014
GP/consultant information sheets or letters	1	22 September 2014
Interview schedules or topic guides for participants	1	14 July 2014
IRAS Checklist XML [Checklist_18082014]		18 August 2014
IRAS Checklist XML [Checklist_24092014]		24 September 2014
Letter from sponsor	1	30 July 2014
Letters of invitation to participant	2	22 September 2014
Non-validated questionnaire [Demographics Questionnaire]	1	14 July 2014
Other [Participant Consent Form - TRACKED CHANGES]	2	22 September 2014
Other	2	22 September 2014
Other [PhD Protocol TRACKED CHANGES]	2	22 September 2014
Other [PIS - TRACKED CHANGES]	2	22 September 2014
Participant consent form	2	22 September 2014
Participant information sheet (PIS)	2	22 September 2014
REC Application Form [REC_Form_18082014]		18 August 2014
Referee's report or other scientific critique report	1	14 July 2014
Research protocol or project proposal	2	22 September 2014
Research protocol or project proposal	1	14 July 2014
Summary CV for Chief Investigator (CI) [Prof Robert Sewell]	1	30 July 2014
Summary CV for student [Paul Cross]	1	30 July 2014

## Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

## After ethical review

### Reporting requirements

The attached document “*After ethical review – guidance for researchers*” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports



- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

### **User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

### **HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at

<http://www.hra.nhs.uk/hra-training/>

<b>14/LO/1589</b>
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<b>Please quote this number on all correspondence</b>
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With the Committee's best wishes for the success of this project.

Yours sincerely



**pp Prof David Russell-Jones**  
**Chair**

Email: [nrescommittee.secoast-surrey@nhs.net](mailto:nrescommittee.secoast-surrey@nhs.net)

*Enclosures:* "After ethical review – guidance for researchers" [\[SL-AR2\]](#)

*Copy to:* Mrs K Ignatian, [karen.ignatian@gstt.nhs.uk](mailto:karen.ignatian@gstt.nhs.uk)

Research & Development  
 16th Floor Tower Wing  
 Guy's Hospital  
 Great Maze Pond  
 London SE1 9RT  
 Tel: 020 7188 7188

Mr Paul Cross  
 Guy's and St Thomas' NHS Foundation Trust  
 15th floor, Tower Wing  
 Great Maze Pond  
 SE1 9RT

07/11/2014

Dear Mr Paul Cross

**Title:** Developing and validating a semi-quantitative model for the benefit-risk assessment of medicines, incorporating patient views as key criteria in decision making

In accordance with the Department of Health's Research Governance Framework for Health and Social Care, all research projects taking place within the Trust must receive a favourable opinion from an ethics committee and approval from the Department of Research and Development (R&D) prior to commencement.

- **R&D Number:** RJ114/N309
- **Ethics Number:** 14/LO/1589
- **Sponsor:** Cardiff University
- **Funder:** N/A
- **End Date:** 30/09/2016
- **Protocol:** 2.0
- **Site:** Guy's & St Thomas' NHS Foundation Trust
- **R&D Approval Date:** 07/11/2014
- **Chief Investigator:** Prof Robert Sewell

NHS permission for the above research has been granted on the basis described in the application form, protocol and supporting documentation as listed in the ethics letter of favourable opinion letter dated I am pleased to inform you that we are approving the work to proceed within Guy's and St Thomas' NHS Foundation Trust and that the study has been allocated the Trust R&D registration number **RJ114/N309**. I can confirm that from the SSI application form you have agreed to recruit 50 within 2 years.

Latest updated documents include:

Document	Version	Date
<b>Protocol</b>	2	22/09/2014
<b>Participant Consent Form</b>	2	22/09/2014
<b>Participant Information Sheet</b>	2	22/09/2014

The research sponsor or the Chief Investigator, or the local Principal Investigator, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.

Whilst the Trust takes on non funded research without charge for sponsorship, research management and governance or research costs we encourage all research to be funded and particularly encourage UKCRN portfolio eligible research. Prior to your next research proposal please contact the R&D department about portfolio eligibility and how to gain funding for research so as to ensure that the study can gain appropriate funding prior to your research application.

#### **Conditions of Approval:**

- The principal investigator must ensure that the recruitment figures are reported.
- The principal investigator must notify R&D of the actual end date of the project.
- R&D must be notified of any changes to the protocol prior to implementation.
- The project must follow the agreed protocol and be conducted in accordance with all Trust Policies and Procedures especially those relating to research and data management.
- Members of the research team must have appropriate substantive or honorary contracts with the Trust prior to the study commencing. Any additional researchers who join the study at a later stage must also hold a suitable contract.

#### **Data Protection:**

Please ensure that you are aware of your responsibilities in relation to The Data Protection Act 1998, NHS Confidentiality Code of Practice, NHS Caldicott Report and Caldicott Guardians, the Human Tissue Act 2004, Good Clinical Practice, the NHS Research Governance Framework for Health and Social Care, Second Edition April 2005 and any further legislation released during the time of this study.

The Principal Investigator is responsible for ensuring that Data Protection procedures are observed throughout the course of the project.

#### **If the project is a clinical trial under the European Union Clinical Trials Directive the following must also be complied with:**

1. The EU Directive on Clinical Trials (Directive 2001/20/EC) and UK's implementation of the Directive: The Medicines for Human Use (Clinical Trials ) Regulations 2004;
2. The EU Directive on Principles and Guidelines for Good Clinical Practice (EU Commission Directive 2005/28/EC); and UK's implementation of the Directive: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006;
3. If a clinical trials team has to keep a subject in a department" out of hours" for whatever reason, the Senior Nurse for the Hospital should be informed of their presence – as should the Resuscitation Team.
4. For CtiMP studies hosted by GSTFT, the sponsor is responsible for reporting updates and providing updated documents related SMPC at this site

#### **Amendments:**

Please ensure that you submit a copy of any amendments made to this study to the R&D Department.

#### **ISRCTN registration:**


If appropriate it is recommended that you register with the Current Controlled Trials website <http://isrctn.org/>. Find out more about registering for an International Standard Randomised Controlled Trial Number (ISRCTN) as part of the Portfolio application process. Non-commercial studies with an interventional component that are eligible for NIHR CRN support can register for an ISRCTN for free via the Portfolio Database.

In line with the Research Governance Framework, your project may be randomly selected for monitoring for compliance against the standards set out in the Framework. For information, the Trust's process for the monitoring of projects and the associated guidance is available from the Trust's intranet or on request from the R&D Department. You will be notified by the R&D Department if and when your project has been selected as part of the monitoring process. No action is needed until that time.

Should you require any further information please do not hesitate to contact us.

Thank you for registering your research project.

Yours sincerely

A handwritten signature in black ink, appearing to read 'SB' followed by several horizontal wavy lines.

Stephanie De Sa Marques Basset  
Research and Development Administrator  
NIHR GSTFT/KCL Biomedical Research Centre

cc: Prof Robert Sewell