

**An Exploratory Case Study of the Physical, Emotional,
and Social Factors that Influence Colorectal Cancer
Patients' Adherence to Oral Chemotherapy Treatment
in South Wales.**

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by

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Dedication

This thesis is dedicated to my late father, Yusuf Ali Ahmed, who passed away on May 4th, 2012. For me and the rest of the family, you continue to be our inspiration. May God show you mercy and grant you eternal peace in paradise.

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Abstract

Introduction: Colorectal cancer is the second most prevalent cancer in men and the third most prevalent in women in Wales. The increased use of oral chemotherapy agents and the convenience it brings to a patient's routine have shifted treatment management closer to home, providing greater patient autonomy. Poor adherence remains a key barrier to achieving optimal treatment outcomes. The aim of this South Wales study was to explore the factors that influence colorectal cancer patients' adherence to oral chemotherapy medicines and examine their beliefs about medication-taking.

Method: Patients diagnosed with colorectal cancer and prescribed oral chemotherapy medications were recruited from an outpatient clinic. An exploratory single case study was used with two embedded units of analysis. Patient questionnaires (n=59) collected data including sociodemographic characteristics, self-reported adherence, and beliefs about medicines. A purposive sample of participants were followed up for semi-structured interviews (n=16) to explore their experiences and challenges with medication adherence. Transcripts were analysed using the framework method of analysis.

Results: Self-reported adherence using the Medication Adherence Report Scale (MARS) indicated high adherence scores to oral chemotherapy agents. The Beliefs about Medicine Questionnaire (BMQ) indicated that patient beliefs in treatment necessity outweighed their concerns (99.3% vs. 44.1%). The Framework method of analysis identified five themes: therapy-related, patient-related, condition-related, healthcare system-related, and socioeconomic-related factors. Medication non-adherence was primarily related to forgetfulness and the adverse effects of oral chemotherapy agents. The findings also revealed that participants experienced negative emotions and identified contributing factors on medication-taking behaviours, including medication side effects, initial distress after learning about treatment needs, forgetting a dose, and malaise about the effectiveness of the medicine.

Conclusion: CRC patients should be made aware of how to recognise potential side effects early, as timely management may prevent non-adherence to the oral chemotherapy medication. Clinicians should be mindful of patient preferences, promote practical methods for remembering to take medication doses, and engage in constructive conversations about information available online. Specific limitations of the MARS scale and its applicability to the CRC patient population were identified. Patients from deprived communities and/or those experiencing negative emotions require an interventional approach targeting areas such as medication beliefs, financial and welfare support, family and social support, and health awareness. This study also implies that developing a pre-screening tool to identify medication-related issues and psychological distress may help patients most in need of additional information, education, and adherence support.

Abbreviations

ACPGBI	The Association of Coloproctology of Great Britain and Ireland
AR	Adherence Rate
BMQ	Beliefs about Medicine Questionnaire
CCI	The Charlson Comorbidity Index
CRC	Colorectal Cancer
CS-SRM	Common-Sense Self-Regulation Model
COVID-19	Coronavirus disease
FACT-G	Functional Assessment of Cancer Therapy-General
5-FU	5-Flourouracil
GLOBOCAN	Global Cancer Observatory
HCRW	Health and Care Research Wales
HBM	Health Belief Model
HFS	Hand-Foot Syndrome
IRAS	Integrated Research Application System
IV	Intravenous
KESS2	Knowledge Economy Skills Scholarship
LHB	Local Health Board
MARS	Medication Adherence Report Scale
MARS-A	Medication Adherence Report Scale for Asthma
MEMS	Medication Electronic Monitoring System
MeSH	Medical Subject Headings

MHRA	Medicines and Healthcare products Regulatory Agency
MMAS	The Morisky Medication Adherence Scale
MPR	Medication Possession Ratio
NCF	Necessity Concerns Framework
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCA	Oral Chemotherapy Agent
OCM	Oral Chemotherapy Medication
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RPSG	Royal Pharmaceutical Society of Great Britain
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TFTD	Trifluridine-Tipiracil Hydrochloride
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WHO	World Health Organisation
WIMD	Welsh Index of Multiple Deprivation

Chapter One

Background

1.1 Introduction

The first chapter provides a brief outline of the researcher, a brief overview of the socioeconomic inequalities in South Wales, and the colorectal cancer incidence, mortality, and survival rates. The growing demand for cancer services as the population ages, combined with current resource constraints, necessitates the reconfiguration of health services. One of the solutions is to move cancer treatment closer to home, which has intensified since the coronavirus outbreak. However, patients with colorectal cancer face new challenges, including adherence to oral chemotherapy medicines. To provide context for the study, the chapter moves on to present an overview of the development of oral chemotherapy medicines and the conceptual issues of medication adherence. The chapter concludes with a theoretical model to conceptualise the factors that influence adherence to oral chemotherapy medicines.

1.2 The Researcher

During my time as a pre-registration pharmacist in a community health centre in South Wales, I became absorbed in identifying medication problems to help people get the most benefit from their medicines and live healthier lives. Since qualifying as a pharmacist, I've worked mainly in primary care in Wales, where I've observed that community pharmacists are easily

accessible and frequently the last healthcare professionals that individuals consult before taking their medication.

My experience conducting patient counselling through medication use reviews has highlighted the challenges with adherence to chronic long-term therapies. The medicines use review service is a structured meeting with patients to identify any problems they may be having with their medicines and, where necessary, provide them with information and support to help them better understand and use their prescription medicines. It has taught me that individuals have different reasons for having difficulties with medication adherence. For example, with newly prescribed medicine users, knowledge-based aspects dominate the consultation, whereas motivation is the biggest barrier to persisting on the regimen. Other examples include holding negative beliefs about a medication after reading about it, speaking with family or friends about it, or experiencing side effects from it. I have witnessed first-hand how much medication is wasted when patients return medicines to the pharmacy, which emphasises the extent of the problem and raises concerns about the possible impact on their health.

Currently, community pharmacists are not directly involved with cancer care, but, based on my experience, cancer patients are increasingly visiting pharmacies for advice about their treatment due to the ease of access. For example, new side effects, supplements that can be taken in conjunction with their oral chemotherapy treatment, or advice on drug interactions with newly prescribed medications. Furthermore, community pharmacists already provide a bowel cancer preventive service, and Public Health Wales and Bowel Cancer UK have run

several campaigns to raise awareness of bowel cancer screening in Wales (NHS Wales 2014; Bowel Cancer UK 2022). However, this is not necessarily relevant to cancer patients who are currently being treated. Pharmacists are trained in the signs and symptoms to look for when their patients present with atypical symptoms or a combination of symptoms. As a result, I was interested in expanding my knowledge beyond the symptom and awareness-raising roles to incorporate adherence support for colorectal cancer patients receiving oral chemotherapy treatment. Regular patient contact provides many opportunities to identify and follow up on patient adherence issues. With these views and experiences in mind, I undertook research regarding the factors that influence adherence to oral chemotherapy medication among colorectal cancer patients.

1.3 Colorectal Cancer in South Wales: Socioeconomic Inequalities

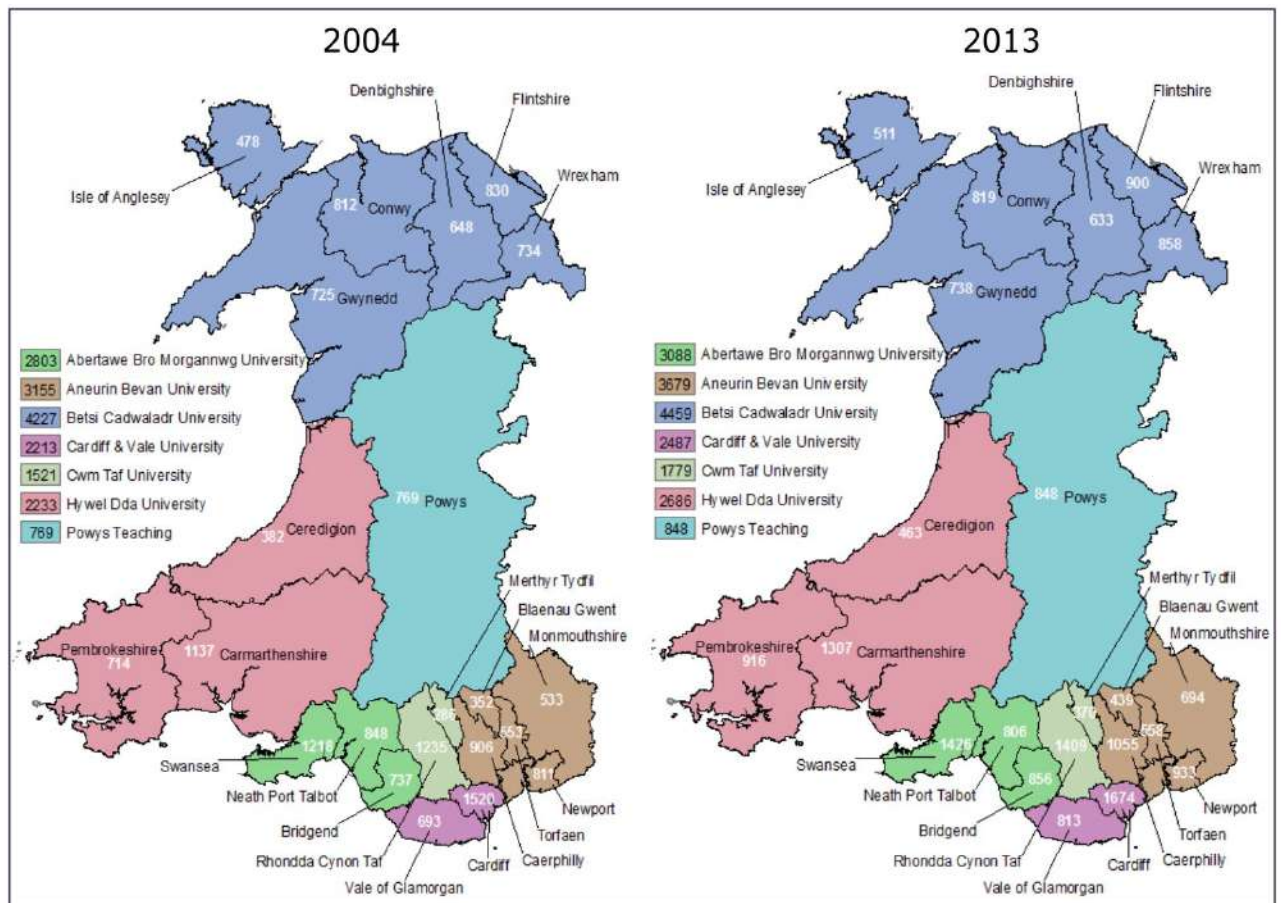
The South Wales region accounts for roughly 30% of the Wales population (Welsh Government 2016). The Valleys are characterised by a huge population of people – more than one quarter of the population – who have a limiting long-term illness, with the problem being particularly acute in more deprived areas such as Merthyr Tydfil, Blaenau Gwent, and Neath Port Talbot (ACPGBI 2016). People in the Valleys also perceive themselves to be in poorer health than their peers in other parts of Wales and in comparative locations. Low economic activity rates, which are a major underlying factor in the lower gross domestic product (GDP) rates per person in Wales, are one of the region's main concerns (Welsh Assembly Government 2004). This intertwines and creates a range of other issues, such as income, health, education, employment, and economic deprivation. The closure of steel and iron industrial estates has resulted in a significant decline in low-wage incomes, which have been

replaced by engineering, food processing factories, and low-tech businesses (Welsh Assembly Government 2004). Despite ongoing efforts to reduce unemployment, the South Wales valleys continue to experience high levels of economic inactivity as well as other socio-economic concerns that are proving difficult to resolve. Many health risk factors, such as smoking, obesity, alcohol, and physical inactivity, are specifically linked to socioeconomic deprivation, and it is one of the most influential factors driving inequalities in cancer incidence, screening, and outcomes in the UK (Cancer Research UK 2020). The Welsh Government, local health boards, and healthcare services all have a part to play in reducing the factors that underpin these conditions, as well as addressing disparities in cancer incidence and mortality rates and long-term health outcomes.

Following a report showing regional inequalities in cancer survival, the Calman Hine report (1995) to the Chief Medical Officers in England and Wales recommended that improvements be made to cancer services in order to ensure equal access to treatment for all patients (Expert Advisory Group on Cancer 1995). Coleman et al. (2004) examined national trends and socioeconomic inequalities in cancer survival during the 1990s for patients diagnosed with one of the 20 most common cancers. Although survival rates rose for both sexes during the 1990s, it was shown that for several cancers, the survival rates improved more in the affluent areas than in the more deprived ones. In reality, during the 1990s, the cancer survival gap between the different socioeconomic groups widened (Coleman et al. 2004). The NHS Cancer Plan (2000) aimed to tackle this by improving prevention, early diagnosis, and treatment plans for all patients, therefore bridging the gap between the affluent and deprived areas (Department of Health 2000). Rachet et al. (2010) assessed the socioeconomic inequalities in cancer survival after the NHS Cancer Plan in England among adults diagnosed with one of 21

common cancers between 1996-2006. The results extend the outcomes seen in the Coleman et al. (2004) study, whereby survival for patients in deprived areas was significantly lower than in affluent areas in both sexes (Rachet et al. 2010). The causes of the disparity in socioeconomic inequalities were not clear, despite the fact that various factors, such as healthcare systems and ethnic disparities, are known to play a role (Dixon et al. 2003; Ward et al. 2004).

Figure 1.1 – change in the number of new cases of cancer in Wales at local authority and health board level (2004-2013) (WCISU 2015).



Source: Welsh Cancer Intelligence and Surveillance Unit's Cancer Registry www.wcisuwales.nhs.uk

In 2015, the Welsh Cancer Intelligence and Surveillance Unit (WCISU) released a report on the cancer incidence, mortality, and survival in the Welsh population, highlighting the wide range

of socioeconomic inequalities, particularly in South Wales and the surrounding valleys region. It also emphasised that cancer incidence rates vary greatly between health boards and local authorities (as shown in *figure 1.1*). When comparing the least and most deprived areas in South Wales, there is a significant difference in the incidence of colorectal cancer, with only lung cancer showing a larger gap in the five-year survival rate; however, the deprivation gap for one-year survival is wider for colorectal cancer (WCISU 2015). There is a lower incidence rate in selective areas of affluence in South Wales (e.g., Monmouth). The colorectal cancer mortality rates by area in Blaenau Gwent are 12% higher than the national average in Wales, whereas the rate in Monmouth is 16% lower (WCISU 2015). The highest incidence rates, however, can be found in Merthyr Tydfil, Newport, and Torfaen, as well as throughout much of South Wales's valleys.

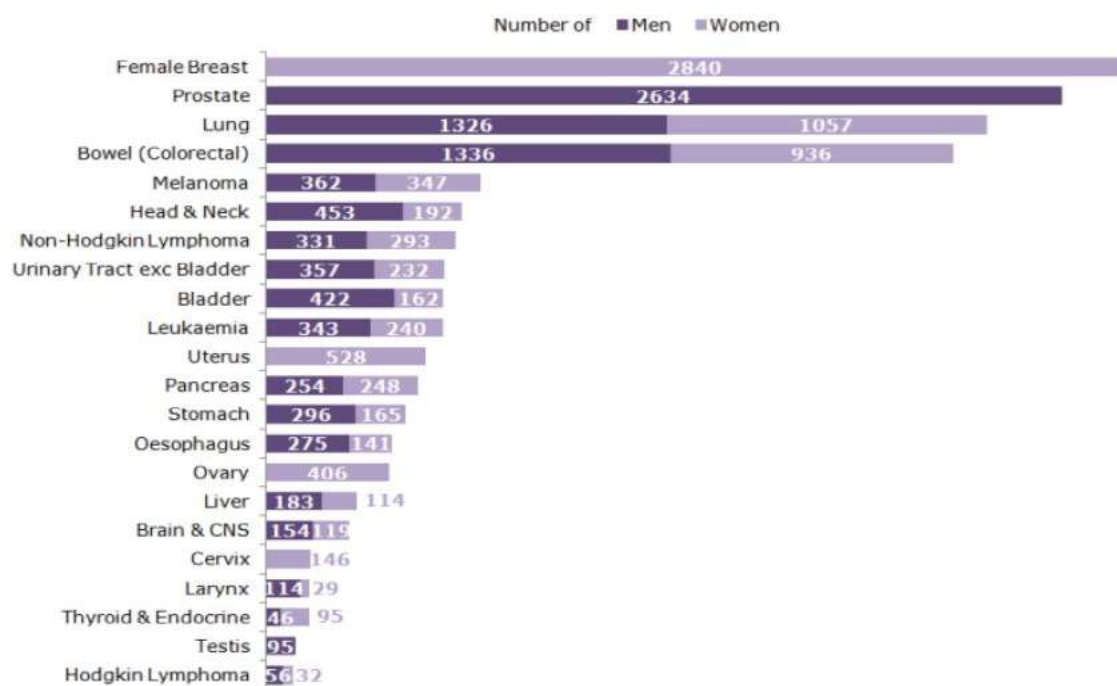
1.3.1 Colorectal Cancer: Incidence, Mortality and Survival Rates

Colorectal cancer (CRC) incidence and mortality rates have been steadily rising in recent years around the world. 1.93 million new cases of CRC were diagnosed in 2020, with 935,000 fatalities, according to GLOBOCAN (2020) forecasts from the International Agency for Research on Cancer (Sung et al. 2021). CRC is the third most common cancer in the world, accounting for 10% of all cancer cases, and the second highest cause of cancer-related death, accounting for 9.4% of all cancer-related fatalities (Globocan 2020).

The number of new cases in Wales continues to rise in both men and women, increasing by more than 12% in 2013 compared to 2004 (WCISU 2015). CRC is the second most common cancer in men and the third most common cancer in women in Wales, as shown in *figure 1.1*

(WCISU 2015). With over 40,000 new cases identified each year, it is one of the most prevalent cancers in the United Kingdom (NICE 2011). CRC is also the second-most common cause of cancer-related deaths in Wales, accounting for 907 deaths in 2013. It has shown one of the largest increases in the last ten years, with men accounting for nearly two-thirds of the increase (WCISU 2015).

Figure 1.2 – The most common cancers in Wales in men and women (WCISU 2015).



The causes of the rise in colorectal cancer incidence and mortality rates, particularly in Wales, are complex, but they include an ageing population as well as changes in the prevalence and distribution of the primary cancer risk factors, several of which are associated with socioeconomic disparities. Wales has the greatest proportion of people over 75 in the UK, as well as the highest proportion of disabled adults under the age of retirement (ACPGBI 2016). Age-specific colorectal cancer incidence rates have risen for both men (over 45 years) and women (over 40 years) (WCISU 2015). CRC is a disease that is influenced by sociodemographic

differences and cultural barriers, with men having a greater sex-specific incidence and mortality rates (Brenner et al. 2007; Nguyen et al. 2009; WCISU 2015b). White et al. (2018) looked at national UK statistics for CRC to see if there were any sex differences and came to the conclusion that males have higher mortality rates due to biological differences and gender-related behavioural factors. For example, alcohol use is more likely to be heavier in men, and there is evidence of a link between alcohol consumption and CRC mortality (Cai et al. 2014). Smoking has long been known to be a risk factor for CRC, with a meta-analysis of prospective studies showing that current or past smokers have a considerably higher risk of CRC incidence and mortality than non-smokers (Liang et al. 2009; Chang et al. 2014). Furthermore, a meta-analysis of cohort study findings suggests that each 100 g of red and processed meat consumed each day increases the risk of CRC by 12% (Vieira et al. 2017). Dietary and lifestyle factors that influence the development of CRC incidence rates, however, are modifiable through public health strategies that promote healthy eating habits, smoking cessation, and reduced alcohol consumption.

1.3.2 Colorectal Cancer Screening: Improving Survival through Early Detection

Early cancer detection is important because survival rate is closely related to cancer development stages. Bowel Screening in Wales provides faecal occult blood screening for people in Wales aged 58 to 74 years old in order to prevent the disease from spreading (NHS Wales 2022). However, in 2016, 54% of people in Wales participated in bowel cancer screening, compared to 72% for breast cancer screening and 77% for cervical cancer screening (Bowel Cancer UK 2018). The 2021 Cancer Awareness Measure survey found that the primary reasons people didn't get their bowels checked were because the test was too messy, they

didn't have any symptoms, and that they were embarrassed (Cancer Research UK 2021). While the uptake of bowel screening tends to be lower in men (White et al. 2018), there have been reports of gender-specific issues among women regarding the uptake and acceptability of the test. These issues include an anticipated greater level of discomfort, anxiety, and embarrassment from the test, as well as the gender of the practitioner who will be conducting the test, which appear to be particular barriers (Wardle et al. 2005).

Factors relating to men's relatively lower participation in screening, especially given their higher overall risk of CRC, has been linked to their lack of understanding about their condition and screening when compared to women. A recent study conducted in England and Wales investigating cancer survival found evidence of inequalities across education and income groups for men with CRC survival (Ingleby et al. 2022). This study suggests that individual and area-level deprivation exert different effects on cancer survival that should be considered. For instance, individuals who have low education levels may have difficulty navigating the NHS health system and understanding their treatment options due to a lack of health literacy. Knowledge, attitudes, and values, masculinity attributes, communication, and resources were all identified as being important factors in a review that studied the factors that influence health screening uptake in men (Teo et al. 2016). Knowledge about health and screening, which in turn influences men's perceptions of the risks to their own health and benefits of screening, was reported as having the greatest influence on attendance at health screenings. Individuals chose not to know about their current health status as they didn't think they were at risk because they didn't have symptoms or a family history of the disease) or because they were afraid of getting a diagnosis.

An additional aspect that influences health-seeking behaviour is the impact of social norms in determining what motivates men to undergo CRC screening. Sieverding et al. (2010) evaluated the role of social norms in the context of men's cancer screening intentions and behaviours among prostate and CRC patients. It was not just influenced by what they believe their family or friends expect them to do (i.e., subjective norm), but also by their perceptions of how other men with similar characteristics behave with regard to cancer screening (i.e., descriptive norm). The interplay between these two social factors, according to the researchers, shows that in the absence of family or friend support to encourage screening, men may be influenced even more by what other men their age do.

Patients who are diagnosed with CRC at a later stage (stages 3 or 4) have a survival rate that is much lower than patients who are diagnosed at an earlier stage (stage 1), with nearly all patients who are diagnosed early surviving (Bowel Cancer UK 2018). The advanced stage at which patients are diagnosed is one of the factors that contributes to the difference in survival rates and the high number of fatalities caused by CRC around the world (Xi and Xu 2021). In addition, people from more deprived populations are less likely to recognise signs and symptoms of cancer than those in the least deprived populations (Niksic et al. 2015). When the symptoms of CRC appear, such as rectal bleeding, anaemia, or stomach pain, most individuals will have cancer that has progressed to an advanced stage in which the disease is malignant, aggressive, and has spread.

1.3.3 Meeting the needs of people with colorectal cancer and the impact of COVID-19

The Welsh government prioritises cancer treatment and remains committed to delivering the best possible care and support to everyone affected by cancer. *The Quality Statement for Cancer* (2021), which replaces the *Cancer Delivery Plan* (2016) for Wales, intends to address the growing demand for cancer services as current resource constraints necessitate service reconfiguration due to the growing and ageing population. The disparity in cancer incidence and mortality between Wales most and least deprived areas lies at the heart of service quality improvement. The quality attributes of cancer care in Wales strive to provide patients with more equal access, allowing people to co-produce their treatment based on what is important to them, their beliefs, aspirations, and circumstances. Cancer services should also interact through the clinical network to be more open, promote equal access, and keep care standards the same (Welsh Government 2021).

The COVID-19 outbreak has had a significant impact on cancer services, with many patients facing delays in diagnosis and treatment (Kutikov et al. 2020). Shortages of intensive care beds and social distancing measures to prevent the transmission of the virus have been common pressures on healthcare services (Alom et al. 2021). Some facilities imposed limits on the number of patients allowed onsite for clinical visits at any given time to reduce preventable deaths due to resource overload (Ferguson et al. 2020). To deal with the disruptions, cancer care centres have had to make significant changes to their service arrangements in order to deliver timely and effective care (Kutikov et al. 2020). In a systematic analysis of the effects of COVID-19 on cancer care provision by Alom et al. (2021), service restructuring was identified as one of the core interventions adopted by health institutions. Furthermore,

referrals to GP practises and healthcare centres near the patient's home were made in several studies in order to sustain care continuity, while also reducing patient travel (Indini et al. 2020; de Marinis et al. 2020). As a result, the coronavirus outbreak has accelerated the need to move cancer services and treatment closer to the patients' homes.

1.3.4 Summary

The number of new CRC cases in Wales continues to climb, and there is variation in colorectal cancer incidence between the least and most deprived areas in South Wales. Socially deprived communities are at higher risk of late-stage diagnosis and, as a result, have poorer health outcomes, contributing to the difference in mortality and survival rates. The growing demand for health services as the population ages, the increasing incidence and prevalence of disease and new treatments, and the desire to improve health outcomes all occur in the context of an unprecedented period marked by the COVID-19 outbreak and limited health-care resources.

In the following section, the oral chemotherapy agents used to treat CRC will be discussed, including treatment options such as oral capecitabine, which is an adjuvant treatment option for late-stage colorectal cancer. Moving CRC treatment closer to home is one solution, and it is also a remit of the Velindre Transforming Cancer Services Programme (Velindre NHS Trust 2016). This is, in part, enabled by the development of oral chemotherapy agents to treat colorectal cancer. The convenience it gives to a patient's routine provides them with more autonomy but also because patients prefer to take their medication orally (Eek et al. 2016). According to Schneider et al. (2019), as a result of technological advancements, cancer

patients' life expectancies have increased significantly, and the disease, and hence the therapies, have shifted from acute to chronic long-term treatments. However, patients who are living with chronic cancers face significant new challenges, such as adherence to oral chemotherapy medicines.

1.4 Development of Oral Chemotherapy Medication

Oral administration of chemotherapy agents has grown in relevance during the last decade. Chemotherapy has traditionally been administered intravenously (IV) in a controlled outpatient hospital setting, but this has since shifted to home-based treatment. Modern advances in cancer treatment since the 1990s have also seen the development and enhanced use of oral chemotherapy medications. Oral administration is currently an option for around one quarter of the cytotoxic chemotherapy drugs (Findlay et al. 2008; Bassan et al. 2014). Additionally, approximately half of all novel cancer treatments under research and development are in the form of oral chemotherapy medicines (Spoelstra and Given 2011). Orally administered chemotherapy agents offer clinicians the opportunity to treat patients without the costs that are often associated with infusion pumps and parenteral treatments.

1.4.1 Oral Chemotherapy agents used to treat colorectal cancer

Chemotherapy can be used in one of three ways to treat colorectal cancer: either *before surgery* (in combination with radiotherapy to shrink the tumour), *after surgery* (adjuvant chemotherapy to reduce the risk of the cancer recurring), or as *palliative chemotherapy* (to slow the spread of cancer and help control the symptoms) (NHS 2022). Adjuvant chemotherapy, for example, is a type of treatment used to treat colorectal cancer that

involves the use of chemotherapy drugs after surgery, in order to reduce the risk of the cancer recurring. Adjuvant chemotherapy is an established treatment for patients with stage III colorectal cancer (Van Cutsem et al. 2001; Hoff et al. 2001; NICE 2011). In some cases, it may also be recommended for patients with stage II colorectal cancer, especially if their other high-risk factors present, such as poorly differentiated tumours or tumours with invasive features. The type of oral chemotherapy treatment that is administered and/or prescribed can differ depending on the nature of the cancer condition, whether the cancer has spread to other vital organs in the body, and where in the body the cancer is located.

The choice to use oral chemotherapy medication should be decided jointly by the patient and the clinicians in charge of their treatment (NICE 2011). Following an informed discussion that considers the individual's clinical condition and preferences, in addition to the contraindications and side-effect profile of the oral agent, the treatment choice should be selected.

1.4.1.1 Capecitabine

Capecitabine (Xeloda® Roche), an oral prodrug of 5-fluorouracil (5-FU), was the first oral chemotherapy medication to be approved by the European Commission in February 2001 for the adjuvant treatment of patients after surgery for stage III (Dukes' C) colon cancer (European Commission 2019). Oral capecitabine is absorbed by the gastrointestinal tract, and it concentrates largely in tumour tissue as opposed to healthy tissue and plasma, which is in contrast to the parentally administered 5-FU (Schuller et al. 2000; Ershler 2006).

In the United Kingdom (UK), the use of capecitabine has been approved both as a first-line treatment for patients with metastatic colorectal cancer and as an adjuvant treatment for patients with advanced colon cancer (NICE 2011). As a first-line treatment for patients' who have metastatic CRC, it is typically used in combination with oxaliplatin, which is also known as XELOX. Capecitabine can also be used as a monotherapy option for the adjuvant treatment of stage III (Dukes' C) colon cancer.

Administration

Capecitabine's recommended dose and dosing schedule are based on clinical evidence, including two large phase 3 trials comparing capecitabine versus bolus IV 5-FU plus leucovorin (LV) (Van Cutsem et al. 2001; Hoff et al. 2001). The most recent NICE guidelines (2022) recommend a starting dose of capecitabine monotherapy for indications of metastatic CRC and stage III colon cancer in adults of 1.25 g/m² twice daily for 14 days, with subsequent courses to be repeated after a 7-day interval. In combination therapy, doses in adults should be 0.8-1 g/m² twice daily for 14 days, with subsequent courses to be repeated after a 7-day interval.

Safety and Efficacy Profile

The efficacy profile of capecitabine was initially assessed in two identical trials. In non-blinded, randomised phase 3 trials, capecitabine monotherapy was compared to intravenous 5-FU with leucovorin (LV) in the first-line treatment of patients with metastatic CRC (Van Cutsem et al. 2001; Hoff et al. 2001). Using data from the two phase 3 trials, Van Cutsem et al, (2004) conducted an integrated follow-up analysis to evaluate the efficacy of capecitabine.

They observed that it was linked with a considerably greater overall response rate than IV 5-FU with LV (26% vs. 17%).

A study conducted by Cassidy et al. (2002) evaluated the safety profile of capecitabine using the phase 3 trials. They discovered that the oral chemotherapy agent had a superior safety profile, with a significantly lower incidence of adverse effects such as diarrhoea, stomatitis, nausea, alopecia, and grade 3 or 4 neutropenia toxicities. Nevertheless, the NICE guidelines (2022) recommend that the dose of oral capecitabine be adjusted according to the tolerability of each patient. An analysis of safety data from three randomised phase 3 clinical trials revealed geographical differences in oral capecitabine tolerability profiles (Haller et al. 2008). A greater number of patients in the United States reported experiencing grade 3 or 4 toxicities than the rest of the world. According to Haller et al. (2008), regional disparities may be attributed to a variety of factors, including cultural differences in patients' behaviour, who feel that some patients are more willing to continue therapy while enduring side effects. Differences in dietary folate consumption may have played a role, as this can increase capecitabine's effects and, as a result, the likelihood of adverse effects (Lewis et al. 1999; Haller et al. 2008).

Capecitabine has also been used as part of combination regimens with several drugs, including oxaliplatin, irinotecan, bevacizumab, and cetuximab, in the treatment of metastatic CRC. Guo et al. (2016), conducted a meta-analysis in which they compared capecitabine with oxaliplatin (XELOX) and IV 5-FU with LV plus oxaliplatin (FOLFOX). The researchers found that there were no statistically significant differences between the two treatments in terms of overall response rate, progression free survival, and overall survival. However, when

compared with Folfox, XELOX was associated with a higher incidence of side effects such as thrombocytopenia, hand-foot syndrome, and diarrhoea.

Despite the proven safety profile of capecitabine, the proportion and severity of toxicities (grade 3 or 4 adverse effects) are still an important issue. Hand-foot syndrome, diarrhoea, stomatitis, nausea, vomiting, alopecia, and fatigue were the most commonly reported adverse effects in the randomised phase 3 clinical trials (Van Cutsem et al. 2001; Hoff et al. 2001). Furthermore, a review of capecitabine by Walko and Lindley (2005) found that over 25% of the 758 patients with breast or colorectal cancer enrolled in three trials experienced adverse effects that included anaemia, diarrhoea, hand-foot syndrome, nausea, vomiting, fatigue or weakness, abdominal pain, and dermatitis. Treatment-related toxicity can lead to dose reductions, as shown in 40.5% and 27.3% of patients in the capecitabine arm of the two trials, respectively (Van Cutsem et al. 2001; Hoff et al. 2001). Cancer-related fatigue, which is characterised by feelings of severe tiredness that do not improve with rest, can impair patients' quality of life at various stages of cancer (Sá Lilian et al. 2015). This is also true of common skin reactions to chemotherapy treatment, such as hand-foot syndrome (HFS), also known as palmar-plantar erythrodysesthesia. HFS is characterised by palmoplantar numbness, tingling, or burning pain and usually coincides with a skin rash that can lead to blisters and ulceration (Kwakman et al. 2020). As a result, NICE (2022) recommends that clinicians monitor patients for severe skin reactions and hand-foot syndrome.

1.4.1.2 Trifluridine-Tipiracil Hydrochloride

Trifluridine-Tipiracil Hydrochloride (Lonsurf[®], Servier Laboratories) is a cytotoxic medicine that combines two active substances: trifluridine, a nucleoside analogue, and tipiracil, a

thymidine phosphorylase inhibitor (European Medicines Agency 2016; Raedler 2016). Trifluridine-tipiracil was approved in the UK in 2016 as a treatment option for adult patients with metastatic CRC who had previously been treated with fluoropyrimidine, oxaliplatin, or irinotecan-based chemotherapies (NICE 2016).

Administration

The trifluridine-tipiracil dosage is calculated depending on the patient's body surface area, and the tablet is provided in two different dosage strengths: 15mg/6.14mg and 20mg/8.19mg. Adults should begin treatment with trifluridine–tipiracil 35 mg/m²/dose given orally twice daily on days 1-5 and days 8-12 of each 28-day cycle for as long as there is a benefit or until there is unacceptable toxicity. There is a maximum limit of 80 mg per dose (Taiho Oncology 2015). The product information sheet also recommends that trifluridine–tipiracil be taken within 1 hour after the morning and evening meals.

Safety and Efficacy Profile

Trifluridine-tipiracil monotherapy was first shown to be clinically effective in pre-treated patients with metastatic CRC in a randomised, placebo-controlled phase 2 trial in Japan (Yoshino et al. 2012). The results demonstrated a substantial difference between trifluridine–tipiracil and placebo in terms of the median overall survival (OS) (Yoshino et al. 2012). This was tested in patients with resistant metastatic CRC or intolerance to prior lines of conventional chemotherapies (including fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab) in an international, randomised phase 3 RECURSE trial (Mayer et al. 2015). The authors found that overall survival (median OS, 7.1 vs. 5.3 months), progression-free

survival (2.0 vs. 1.7 months), and disease control rate were all much better with trifluridine–tipiracil treatment than with placebo (44% vs. 16%).

In the phase 3 trial conducted by Mayer et al. (2015), the safety profile of the trifluridine–tipiracil group was associated with a higher frequency of grade 3 adverse events in comparison to the placebo group (69% vs. 52%). In patients treated with trifluridine–tipiracil, the incidence of grade 3 neutropenia was 38 percent, whereas it was 0 percent in the placebo arm. As a consequence, Lee and Chu (2016) suggest that clinicians should exercise caution when considering dose reductions of trifluridine–tipiracil in patients who present with mild neutropenia. It is recommended that patients have blood counts taken before the start of each cycle as well as on day 15 of each cycle (Taiho Oncology 2015). This is because the onset of grade 3 neutropenia can occur for the first time after the first cycle, as was demonstrated in the phase 3 trial (Mayer et al. 2015). Other studies have also reported the incidence of neutropenia brought on by oral chemotherapy drugs used for the treatment of CRC (Cassidy et al. 2002; Scheithauer et al. 2003).

Additionally, a higher incidence of grade 3 adverse effects such as anaemia, diarrhoea, thrombocytopenia, nausea, and vomiting was identified in the group that received trifluridine–tipiracil (Mayer et al. 2015). Tiredness (fatigue, weakness), nausea, decreased appetite, abdominal pain, and fever are the most common adverse events (all grades) associated with trifluridine–tipiracil (Lonsurf®) (Taiho Oncology 2015). In addition, 14% of the treatment group required dose reductions due to the most common grade 3 or 4 toxicities, which were related to asthenia or fatigue as well as decreased appetite (Taiho Oncology 2015).

There have been no reported drug interactions with this treatment because both active substances of trifluridine and tipiracil are not metabolised by the liver cytochrome P450 enzymes (Taiho Oncology 2015; Lee, J James; Chu 2016). Nevertheless, food reduces the rate and extent of absorption, and it is recommended that the tablet be taken within 1 hour after the morning and evening meals (Taiho Oncology 2015). Therefore, patients should be encouraged to talk to their doctors about things like nutrition and appetite issues that might affect how well they take the oral chemotherapy agent.

1.4.2 Summary

The oral chemotherapy agents capecitabine (Xeloda®) and trifluridine-tipiracil (Lonsurf®) are used to treat metastatic CRC, and the choice to use oral treatment occurs following an informed discussion that considers the individual's clinical condition and preferences. Capecitabine is also used as part of combination regimens with several drugs, including oxaliplatin (XELOX), irinotecan, bevacizumab, and cetuximab, in the treatment of metastatic CRC. Despite the oral chemotherapy agents' documented safety and efficacy profiles, the severity of treatment-related toxicities remains a major concern. For example, capecitabine-related grade 3 or 4 adverse effects (e.g., hand-foot syndrome, diarrhoea, stomatitis, nausea, vomiting, alopecia, and fatigue) and trifluridine–tipiracil-related grade 3 adverse events (e.g., neutropenia, anaemia, diarrhoea, thrombocytopenia, nausea, vomiting, tiredness, nausea, decreased appetite, abdominal pain, and fever).

Medication adherence is becoming of growing interest as the number of CRC patients receiving oral chemotherapy treatment increases. It is important to know whether CRC patients are adhering to their treatment regimen, as support for adherence could be a key component of addressing disparities in health outcomes. In the following section, the conceptual issues of adherence will be discussed, including the definition and classification of adherence to medication, as well as methods of measuring adherence and the implications of poor adherence to oral chemotherapy agents.

1.5 Conceptual Issues of Adherence

1.5.1 Compliance and Concordance

There are many terms used in the literature to describe taking medication correctly according to the instructions on the drug label, such as *adherence*, *compliance*, *concordance*, and *persistence*. Previously, patient compliance and medication adherence were synonymous (Cramer et al. 2008). These terms, while related, have somewhat different meanings. Haynes et al. (1979) provide the most frequently referenced definition of compliance: “*the extent to which a patient’s behaviour (in terms of taking medications, following diets, or executing other lifestyle changes), coincides with medication or health advice.*” The term “compliance” is viewed as having negative connotations because it appears to denote the patients’ role as passively following the doctors’ instructions (Horne, Weinman, Barber, et al. 2005). It appears to imply a one-sided conversation in which the doctor determines the appropriate therapy, and the patient must comply regardless of its suitability. Aside from the negative connotation, there are other issues with the term, as research over the past two decades indicates that

compliance, or lack thereof, is often not fully explained by the sociodemographic characteristics of patients, the complexity of treatment regimens, or personality traits (WHO 2003; DiMatteo 2004). Furthermore, noncompliance is often associated with either the patient's failure to comprehend the treatment regimen or its benefits, or an indication of irrational or maladaptive patient behaviour when he or she refuses to comply (Chakrabarti 2014). In this way, the term “compliance” tends to represent a paternalistic view of medicine use that ignores the patient’s perceptions of medication-taking behaviour. However, the importance of patients' perceptions of illnesses or medication is becoming more widely recognised (Horne and Weinman 1999). Non-compliance on the part of the patient is often the consequence of balancing the need for adequate treatment with concerns about the medication.

In 1995, a committee of the Royal Pharmaceutical Society of Great Britain (RPSG) proposed a term called “concordance” which aimed to re-conceptualise the issue of compliance (Horne, Weinman, Barber, et al. 2005). Concordance is sometimes used incorrectly as a synonym for adherence. However, according to Bell et al. (2007), the term is different in that it refers to the doctor-patient relationship, i.e., their alignment of views, whereas adherence and compliance refer to the patient's medication-taking behaviour. According to this point of view, the patient's perspective is taken into consideration when deciding whether or not to prescribe the medication (Horne, Weinman, Barber, et al. 2005). Despite its advantages, the concept of concordance does not go far enough to address the problem of the tension between prescribing based on scientific evidence and patients' judgments based on their own sentiments.

1.5.2 Definition and Taxonomy of Adherence

The World Health Organization (WHO) defines adherence as *“the extent to which a person’s behaviour, – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendation from a healthcare provider”* (WHO, 2003). The term is meant to be non-judgmental, and it emphasises the importance of both the doctor and the patient participating in a discussion that results in the best medication regimen to be followed.

In later work, Lehane and McCarthy (2007) conducted a review in which they classified what aspects of non-adherence constitute intentional and unintentional features. There is an underlying premise that patients make an active decision to not follow agreed-upon treatment advice from their healthcare providers when it comes to intentional non-adherence. Unintentional non-adherence, on the other hand, is a passive process in which the non-adherence is mostly caused by factors such as forgetfulness, adverse effects, and things they can’t control (i.e., misunderstandings and language barriers).

In recent work, Vrijens et al. (2012) proposed a conceptual foundation following a review to identify the terminology that has been used to describe medication-taking behaviour. As a result of this review, “adherence to medication” was recognised as the most appropriate and explicit terminology for defining the process by which patients take their medication in the manner that is indicated. This was agreed upon following analysis and discussions with international experts at a European consensus meeting that was organised in conjunction

with the European Society for Patient Adherence, Compliance, and Persistence (ESPACOMP).

Figure 1.3: Illustration of the process of adherence to medication as described by Vrijens et al. (2012).

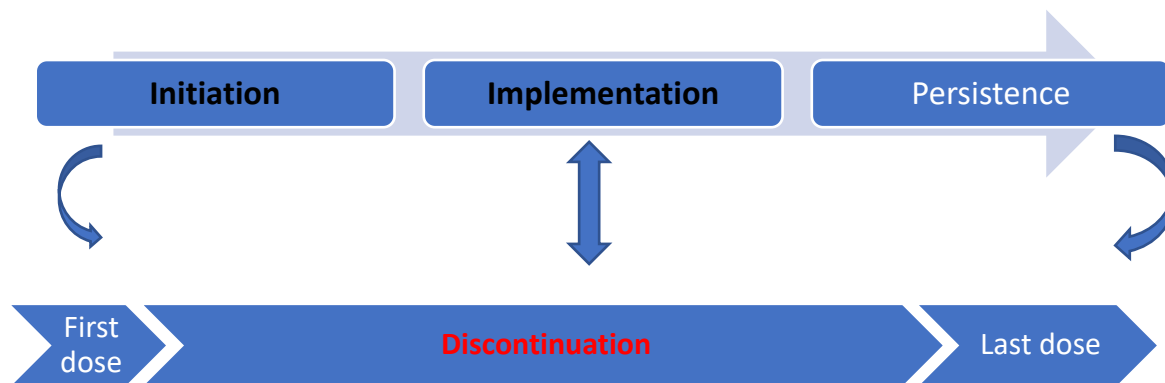


Figure 1.3 shows the three main components by which patients' take their medication as prescribed: initiation, implementation, and discontinuation. The process of adherence to medication begins with treatment initiation when the patient takes the first dose of the medication. From the first dose to the last, the implementation phase is described as the extent to which a patient's actual dosing corresponds to the prescribed regimen. When the next dose to be taken is omitted and no more doses are taken after that, the medication is said to be discontinued, which marks the end of the treatment. Furthermore, persistence is defined as the time interval between the initiation of treatment and the last dose before discontinuation (Vrijens et al. 2012). Vrijens (2012) explains that non-adherence to the medication can occur across all three main components: for example, a late start or non-initiation of the oral chemotherapy treatment, sub-optimal implementation of the dosing regimen, or early treatment discontinuation.

1.5.3 Methods of Measuring Medication Adherence

There is no agreed-upon standard for what constitutes adequate adherence. Osterberg et al. (2005) presented two main methods for assessing adherence: direct and indirect methods (as shown below in *Table 1.1*). Healthcare professionals previously had to rely on estimates based on subjective patient adherence to medication use, despite the fact that such information is prone to recollection difficulties and numerous factors for withholding details (Blaschke et al. 2012).

Table 1.1 – Direct and Indirect Methods of measuring adherence (Osterberg et al 2005).

Test	Advantages	Disadvantages
Direct Methods		
Directly observed therapy	Most accurate	Patients' can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and “white coat adherence” can give a false impression of adherence; expensive
Measurement of the biological marker in blood	Objective: in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect Methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting.	Susceptible to error with increases in time between visits; results are easily distorted by the patients.
Pill Counts	Objective; quantifiable, and easy to perform.	Data easily altered by the patient (e.g., pill dumping).
Rates of prescription refills	Objective; easy to obtain data.	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system.
Assessment of the patient’s clinical response	Simple; generally easy to perform.	Factors other than medication adherence can affect clinical response.
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication.	Expensive; requires return visits and downloading data from medication visits.
Measurement of physiological markers (e.g., heart rate)	Often easy to perform.	Markers may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response).
Patient diaries	Help to connect for poor recall	Easily altered by the patient.

Direct measurements include observing patients take each dose or measuring plasma concentrations to detect drug levels in the blood or urine, with sub-therapeutic levels indicating poor adherence. The direct approach is particularly useful with drugs that have a narrow therapeutic index, such as phenytoin or warfarin, where small variations in dose or blood concentration can cause toxicity (Osterberg et al. 2005). It is, however, expensive and very time-consuming. It can place a strain on patient-provider relationships, and patients can still devise methods of misrepresentation by hiding tablets in their mouths before discarding them after the duration of monitoring (Osterberg et al. 2005).

Indirect methods are relatively inexpensive and take into account the patients' perspectives by discussing the convenience of taking prescribed medication with them and evaluating their clinical responses (Osterberg et al, 2005). Self-reported data from questionnaires, pill counts, and electronic monitoring devices are all examples of this method. Osterberg et al. (2005) state that these measurements can be implemented in a clinical environment, although questioning the patient can lead to misrepresentation and tends to result in the healthcare professional overestimating the patient's adherence. To assess patient adherence to oral chemotherapy medicines, an indirect method will be used given the time limits of this study. This approach is both cost-effective and practical in a clinical setting.

1.5.4 Self-reported Outcome Measures of Adherence

A measure of medication adherence is important in healthcare research because it allows researchers to understand the role of non-adherence on health outcomes. Patients are known to overestimate their level of adherence when using self-reported measures, which is

one of the disadvantages (Horne, Weinman, Barber, et al. 2005). Nevertheless, it is the method that the NICE recommendations consider to be the one that is most appropriate for use in clinical practice (NICE 2009). A large number of self-reported adherence scales have been used in studies on chronic illnesses to elicit information about various aspects of adherence, such as medication-taking behaviour, barriers to and determinants of adherence, and beliefs associated with adherence (Garfield et al. 2011; Nguyen et al. 2014). When choosing an adherence scale, it is necessary to take into account both the characteristics of the scale itself and the degree to which it has been validated.

The Morisky medication adherence scale (MMAS) is one of the most widely used self-report patient questionnaires for assessing medication adherence (Morisky et al. 1986). Morisky et al. devised a self-reported measure consisting of four items to assess common medication-taking behaviours that lead to medication non-adherence. Later in 2008, four new items regarding adherence behaviour were added to the initial version of the MMAS (Morisky et al. 2008). It has seven yes/no questions and one question with a 5-point Likert scale answer.

Table 1.2 Morisky Medication Adherence Scale (8-item MMAS) (Morisky et al. 2008).

	YES	NO
1. Do you sometimes forget to take your medication?		
2. People sometimes miss taking their medications for reasons other than forgetting. Over the past 2 weeks, were there any days when you did not take your medication?		
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring your medication?		
5. Did you take your medication yesterday?		
6. When you feel like your symptoms are under control, do you sometimes stop taking your medication?		
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		

8. How often do you have difficulty remembering to take all your medication? Never/Rarely... Once in a while... Sometimes... Usually... All the time...		
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It was reported by Moon et al. (2017) in a systematic review of the MMAS-8 that the criterion validity may be improved, particularly with item 5, because it was not sensitive enough to medication adherence due to the ‘yes’ response, which makes it difficult to differentiate patient behaviour. Despite this, the MMAS-8 measure has been used in chronic illness studies such as hypertension (Lee et al. 2013; Khayyat et al. 2017), diabetes mellitus (Chew et al. 2015; Jannoo and Mamode Khan 2019), and in cancer patients' receiving oral chemotherapy medication (Berry et al. 2015; Brier et al. 2015).

The medication adherence report scale (MARS) is a self-reported adherence scale developed in the United Kingdom that assesses both intentional (“*I try to avoid using it*”) and nonintentional non-adherence (“*I forget to take it*”), see *Table 1.3* (Horne and Weinman 2002a). It is possible that the wording of questionnaire items may make it difficult to record adherence behaviours accurately (Chan et al. 2019). Horne et al. (2002) employ a statement to lessen the impact of self-presentational bias on reports of adherence. The following statement is prefaced before the list of MARS items: “*Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor said. Here are some ways in which people have said they use their medicine. For each statement, please tick the box which best applies to you*”. The MARS questionnaire asks respondents to rate the frequency with which they engage in each of the adherence-related

behaviours on a 5-point Likert scale. Scores for each item are summed up to give a total score, with higher scores indicating higher levels of adherence.

Table 1.3 The Medication Adherence Report Scale (Horne and Weinman 2002a).

Items	
1	I alter the dose
2	I forget to use it
3	I stop taking it for a while
4	I only use it when I feel breathless
5	I decide to miss out a dose
6	I take less than instructed
7	I avoid using it if I can
8	I use it only as a reserve, if my other inhaler doesn't work
9	I use it regularly every day

The shortened version, i.e., MARS-5, which consists of items 1, 2, 3, 5, and 6, has shown promise as a rigorous tool for measuring patient reports of their medication across a range of health conditions (Chan et al. 2019). The measure was shown to have good reliability and validity across three different long-term conditions: hypertension, asthma, and diabetes. The advantage of the MARS-5 version over the existing version is that it is more practical to use in a clinical setting, without compromising the reliability and validity of the questionnaire, which can serve as a starting point to guide adherence discussions (Chan et al. 2019). It has been used in studies of chronic illnesses such as chronic obstructive pulmonary disorder (Fischer et al. 2018), stroke (Lin et al. 2018) and oral chemotherapy treatment (breast and colorectal cancer) (Bhattacharya et al. 2012a; Kim et al. 2014). The MARS-5 indicates reasons for poor adherence, which might assist in the selection of appropriate interventions tailored to address the specific reasons for non-adherence.

1.5.5 Consequences of sub-optimal adherence

Suboptimal adherence to oral chemotherapy medications has several undesirable implications, including reducing the clinical benefits of the prescribed treatment regimen. In a cohort study, McCowan et al. (2008) reported an association between tamoxifen adherence and poorer survival in 19% of patients who were less than 80% adherent to tamoxifen. Marin et al. (2010) discovered a strong link between imatinib adherence and molecular responses in chronic myeloid leukaemia patients, with 26% of those who were less than 90% adherent to imatinib being less likely to achieve a major or complete molecular response than those who were adherent > 90% of the time. Furthermore, a prospective cohort study that investigated adherence management for patients' with cancer taking capecitabine found that treatment was prematurely discontinued in 33% of initially non-adherent patients due to the growth of their tumours (Krolop et al. 2013).

Approximately 33%-69% of all medication-related hospital admissions in the United States are due to poor medication adherence (Osterberg, Lars; Blaschke 2005). Poor adherence to oral chemotherapy agents has also been associated with poor health outcomes and increased health costs (Foulon et al. 2011). Wu et al. (2010) found that in a real-world comparison of medical visits, costs, and adherence among patients with chronic myeloid leukaemia, individuals that were more adherent to nilotinib used fewer healthcare resources, resulting in cost savings, as compared to dasatinib patients'. Also, even though patients' need to attain high medication adherence to achieve optimal treatment efficacy, the therapeutic benefit derived from oral chemotherapy agents can vary from drug to drug (Schneider et al. 2019). Tamoxifen, for example, has an elimination half-life of 7 to 14 days, whereas capecitabine and

trifluridine-tipiracil have elimination half-lives of approximately 2 hours (Reigner et al. 2001; Kish and Uppal 2016). The narrow therapeutic index of these oral chemotherapy agents means that the consequences of one missed dose may be more severe in a patient than medicines with longer elimination half-lives. Also, improving CRC patients' adherence to oral chemotherapy agents could not only reduce the care load on health systems and improve patients' quality of life, but also slow the disease's development and increase the overall patient survival rate. Given the potential consequences of sub-optimal adherence on health outcomes and survival, it is critical to discuss the factors that may influence adherence in patients receiving oral chemotherapy medications.

1.6 Theoretical Framework: Factors Contributing to Adherence to Oral Chemotherapy Medicines

Theoretical models are useful in conceptualising the factors that influence adherence to oral chemotherapy medicines. Several theoretical approaches have been established to better understand the factors that contribute to medication adherence in particular patient groups or disease conditions. The Health Belief Model (HBM), a widely used psychosocial approach in health behaviour research, is a theory that was initially established in the 1950s by social psychologists working for the United States Public Health Service (Rosenstock 1974; Janz and Becker 1984). The model implies that people's health-related behaviours are dependent on combinations of several factors, including perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, and self-efficacy. The Necessity-Concerns Framework (NCF) is a model that focuses on beliefs that underpin patients' attitudes toward their medication and decisions on whether or not to take their medication (Horne,

Sarah C.E. Chapman, et al. 2013). It was developed to investigate medication adherence and maintains that adherence is the result of a trade-off between a patient's perceived need for the prescribed medication (necessity beliefs) and their concerns about the medication (Horne and Weinman 1999).

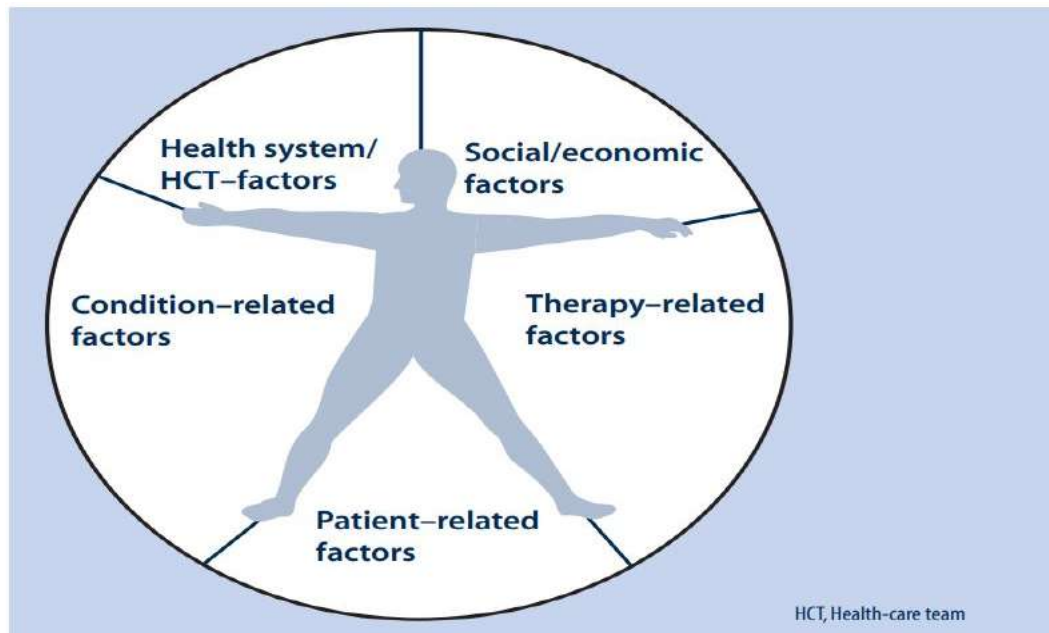
Furthermore, the Common-Sense Self-Regulation Model (CS-SRM) describes how individuals respond to and manage an illness, symptom, or health threat (Leventhal et al. 2003; Leventhal et al. 2016). Self-regulation is applicable to numerous health-related issues, including medication adherence. The coping strategy is determined by the individual's perception of the health hazard; for instance, the identification of a health threat could be an individual's decision not to take their oral chemotherapy treatment because they are uncertain about its benefits (i.e., cognitive behaviour). The individual's response may be characterised by emotional or cognitive behaviour. After the illness representation (i.e., perception) is created, the individual will take action in response to the health threat. This may involve seeking medical advice from a clinician (a positive response) or engaging in denial (a negative response). The CS-SRM describes how, after engaging in a coping activity, individuals will re-evaluate their condition and, if their health status is not satisfactory, they may adjust their illness perception and their plan of action (Leventhal et al. 1998).

While health behaviour theories are helpful in understanding the contribution of patient-related factors to medication adherence, it appears that they are limited in their ability to describe the sum of all adherence-related factors, such as the effect of the health system and healthcare team on patient behaviour towards medication adherence (Ori et al. 2019). Adherence to medication is also a complex behaviour, and to date, more than 400

determinants of oral medication adherence have been identified (Kardas et al. 2013). Therefore, it is reasonable to anticipate that a single-factor approach might have limited success if the factors determining adherence interact and enhance each other's influence (WHO 2003). For example, the capability (or lack thereof) of healthcare teams to educate patients and/or address concerns regarding medication issues by means of the services that are offered and how this may influence the patients' adherence decisions. Consequently, a theoretical model that covers a wider set of determinants would be more suitable for this exploratory case study (*see section 3.3*), since it allows the researcher to immerse himself in a complex setting and does not seek to exclude adherence-influencing elements.

The World Health Organisation (WHO) framework on adherence to long-term therapies is valuable in its emphasis on encompassing a wider set of determinants than only the individual patient (WHO 2003). The WHO framework has proposed utilising a holistic approach to improve medication adherence and identifies five main dimensions (as illustrated in *figure 1.5*) that potentially impact medication adherence: social/economic, patient-related, therapy-related, condition-related, and health system/healthcare team-related factors.

Figure 1.4 The five dimensions of adherence (WHO 2003).



Patient-related factors

Patient-related factors represent the knowledge, beliefs, perceptions, and expectations of the patient. Side effects, expectations, and experiences, as well as illness cognition, all influence personal judgments about whether the medicine is necessary, according to the WHO (2003). Consistent with the WHO report, a recent literature review identified illness perceptions, medication beliefs, health beliefs, and depression as the primary psychosocial determinants of adherence to oral anticancer treatment (Kaptein et al. 2021). Findings from a study on healthcare professionals' opinions of adherence to oral anticancer agents, only 56%, 50%, 28%, and 23% of doctors, nurse practitioners, nurses, and pharmacists, respectively, reported knowing their patients' level of adherence (Verbrugghe, Timmers, Boons, Van Den Bemt, et al. 2016). According to Keating et al. (2010), one of the underlying factors could be that patients are highly adherent owing to the severity of the disease and that the physician-patient relationship naturally leads to adherence. However, patient beliefs about their illness

can be a strong predictor of reported adherence, as shown by the Grunfeld et al.'s (2004) study in breast cancer patients taking tamoxifen. The belief that there was no benefit to be gained from taking tamoxifen was the primary reason for non-adherence. Kaptein et al. (2021) recommend that medication beliefs and illness perceptions be incorporated into adherence programs and encourage healthcare professionals to identify and address adherence-related psychosocial variables.

Furthermore, a systematic review of breast cancer patients identified that characteristics related to perceptual and psychological feelings about illness and medication had significant associations with adherence, similar to Kaptein et al. (Lin et al. 2017). In addition, medication adherence was positively associated with patients' beliefs in the importance and benefits of taking adjuvant endocrine therapy (Jacob Arriola et al. 2014). The study also discovered a positive link between the frequency of physician visits and medication adherence, highlighting the value of patient-centred communication.

Nonetheless, Bender et al.'s (2014) study on the influence of patient and treatment factors on adherence in breast cancer found that participants' concerns about adjuvant endocrine therapy were greater than their belief in the treatment's necessity. The study also found that having a negative mood and experiencing symptoms before starting treatment predicted nonadherence to endocrine medication over time. Depressive symptoms (using the Beck Depression Inventory II) and anxiety (using the Profile of Mood States subscale) were measured in the Bender et al. study, and participants reported higher levels of depressive symptoms and anxiety prior to treatment. The severity of people's negative moods increased over time because of how they felt about their finances, their symptoms, the stage their

condition had reached, and the complex dosing regimens they were following. In addition, anxiety and depression have been linked to higher morbidity and mortality with prescribed medical treatment, and poor adherence is considered to be one of the contributing factors (M. Robin DiMatteo et al. 2000). In a meta-analysis study, DiMatteo et al. (2000) examined recommendations given by physicians and showed that depressed patients were three times more likely to be noncompliant than non-depressed patients. Depression frequently involves a considerable degree of hopelessness (WHO 2003), and when an individual lacks confidence that any action would be beneficial, it may be challenging for them to adhere to the treatment regimen.

Another commonly reported patient-related factor that leads to non-adherence is forgetting to take a dose (Winterhalder et al. 2011; Verbrugghe et al. 2013a; Muluneh, Deal, Maurice D. Alexander, et al. 2018). For example, a Muluneh et al. (2018) study that analysed patients with a variety of different cancers and their use of oral chemotherapy medicines reported that 30% of patients' forgot to take their medication at least sometimes. By bringing oral chemotherapy treatment closer to patients' homes, they will need to remember to take their medicine regularly and on time. In addition, younger and older patients are patient-related characteristics that can influence adherence. In breast cancer patients, patients under the age of 45 had the highest risk of non-adherence to aromatase inhibitors (Sedjo and Devine 2011). Another study on adherence to endocrine treatment found that patients aged between 50 and 74 were more likely to be adherent than those under the age of 50 (Font et al. 2012). Although there is no agreement on the age cut-off that distinguishes patients at risk from those who may be adherent (Ross et al. 2020), some of the differences can be linked to differences in malignancy and the type of oral chemotherapy medication patients receive.

Therapy-related factors

According to the WHO (2003), there are a variety of reasons patients may struggle with treatment adherence, including side effects, frequent changes of medication, the duration of treatment, previous treatment failures, and the complexity of the medical regimen. Side effects of the treatment have been cited as a frequent reason for non-adherence to oral chemotherapy agents (Verbrugghe et al. 2013a; Puts et al. 2014; Greer et al. 2016; Ross et al. 2020). Greer et al. (2016) conducted a systematic evaluation of oral antineoplastic drugs and discovered that treatment factors such as harsher side effects and higher doses of medication were linked to poor adherence. In addition, a recent prospective analysis of capecitabine-treated gastrointestinal patients found that adverse symptoms such as hand-foot syndrome and vomiting were associated with capecitabine adherence (Visacri et al. 2022). Lebovits et al. (1990) found that the greater toxicity level of the oral chemotherapy agent can make it more difficult to adhere to a dosing regimen by causing people to cut back on their intake or by temporarily stopping the treatment.

Adherence to oral chemotherapy agents such as capecitabine and trifluridine-tipiracil, which are administered twice daily with treatment free intervals, can be influenced by the complexity of the regimens. Patients must take on more responsibilities, such as going to clinics regularly, following complex dosing regimens, and self-monitoring symptoms and side effects (Thivat et al. 2013). A nurse-led intervention study to improve adherence and management of symptoms in patients receiving oral chemotherapy agents found that patients on continuous regimens had better adherence than patients on intermittent

regimens (Sandra L. Spoelstra et al. 2013). The study suggested that with oral chemotherapy agents, patients who are less confused about dosing are more likely to adhere to their regimens.

Social and economic factors

The WHO (2003) framework states that low socioeconomic status can create conditions in which patients have to prioritise obligations ahead of treatment, which can have a significant effect on adherence (WHO, 2003). Factors that can have significant effects include a lack of an effective social support network, low levels of education, poverty, illiteracy, unemployment, and unstable living conditions. In the South Wales valleys, socioeconomic deprivation, together with other public health risk factors such as smoking, obesity, alcohol, and physical inactivity, can increase the likelihood of higher cancer incidence rates (WCISU, 2015). According to a recent review on adherence-influencing factors, higher financial status and better socioeconomic standing appear to have a beneficial impact on oral anticancer drug adherence, though belonging to an ethnic minority group may have a negative impact (Gast and Mathes 2019). Furthermore, higher levels of social support have been linked to better medication adherence in individuals using oral anticancer drugs (Mathes et al. 2014). Given et al. (2011) state that family members and caregiver play an important role in patient adherence since they can remind patients to take their medication.

Healthcare team and system-related factors

A positive relationship built between the healthcare provider and the patient can promote adherence (WHO, 2003). Lea et al. (2018) recognised improved patient-provider informed decision-making as a potential for quality improvement in a study that explored adherence behaviours among chronic myeloid leukaemia patients' receiving oral chemotherapy treatment. The study found a drop in adherent responses to questions concerning doctors and nurses working together with patients in making decisions and indicated that healthcare teams should be more involved with patients to improve long-term adherence. Also, in a study about treatment satisfaction and adherence in patients' with diverse malignancies, Jacobs et al. (2017) discovered that individuals who reported improvements in their perceptions of being understood and respected by their oncologists, were involved in healthcare decisions, and had trust in them were more likely to be adherent. Similarly, a number of additional factors have been identified that can influence medication adherence, such as lack of knowledge and training for healthcare providers, short consultations, and the capacity to educate patients about their medication and carry out follow-up procedures (WHO, 2003). Arber et al.'s (2017) study to identify patients' knowledge about their oral chemotherapy medication revealed that patients who were less well informed about their treatment may be at risk of non-intentional non-adherence due to misunderstandings or forgetfulness about timing their medication intake. As a consequence of this, non-adherence can lead to increased use of healthcare and financial resources, greater rates of hospitalisation, and longer stays (Osterberg and Blaschke 2005).

Condition-related factors

Adherence is strongly influenced by condition-related factors such as the severity of the disease and symptoms, the level of disability (physical, psychological, and social), and the availability of effective therapies (WHO, 2003). The 27-item Functional Assessment of Cancer Therapy-General (FACT-G) was used in a study on patient experiences with oral chemotherapy agents to assess their quality of life in a number of domains of well-being (Jacobs et al. 2019). According to the data, patients with a greater number of concomitant medications had a lower quality of life, which could influence their adherence behaviours. There is also evidence from previous studies that has shown a significant correlation between nonadherence to the oral chemotherapy treatment regimen and the number of comedications (Wu et al. 2010; Thivat et al. 2013). Furthermore, the patients' general comorbidities have been shown to be a factor impacting adherence. The Charlson Comorbidity Index (CCI) was used in a breast cancer study that measured the 1-year nonadherence rates of women taking aromatase inhibitors (Sedjo and Devine 2011). Comorbidities, such as heart disease and depression, were found to be related to nonadherence in patients with higher CCI scores.

1.7 Conclusion

This chapter provided an overview of the incidence, mortality, and socioeconomic disparities in colorectal cancer in South Wales. There is a considerable disparity in the incidence of colorectal cancer between the least and most deprived areas in South Wales. Late-stage diagnosis is more prevalent in socially deprived areas, resulting in poor health outcomes and disparities in mortality and survival rates. In addition, the resources available to health

services are becoming increasingly constrained, which has led to the reconfiguration of cancer services.

This chapter presented a brief overview of the oral chemotherapy drugs used to treat CRC and the conceptual issues of medication adherence to contextualise the study. Also, as briefly discussed using the WHO framework's five dimensions and by considering various cancer types, adherence to oral chemotherapy agents is a complex behaviour with many determinants. The following chapter moves on to a review of the literature to understand what is known about the factors that influence adherence to oral chemotherapy medicines among CRC patients and to help guide the study.

Chapter Two

Literature Review

2.1 Introduction

This chapter presents a literature review to understand what is known about the factors that influence adherence to oral chemotherapy medicines among colorectal cancer patients. The chapter commences with a discussion of the methods, including the search strategy, eligibility criteria, and approach to assessing the risk of bias in the included studies. The subsequent findings examine the quality of the evidence on the measures used to assess adherence as well as the factors that influence adherence and the challenges associated with taking oral chemotherapy medicines. It concludes by identifying gaps in the existing knowledge base and setting out the research question, aim, and objectives for the study.

2.2 Overview of the Literature Search

Over the years, theories have been developed to explain the lack of adherence to long-term therapies. Initially, the issue was attributed to patients' difficulties with compliance, but later, the role of the healthcare professional was addressed (WHO 2003). The severity of the disease was thought to motivate patients to take their medication as prescribed (Nilsson et al. 2006; Hugtenburg et al. 2013). It is now evident that a multi-system approach is required to ensure that patient adherence to medication is optimal in the long term (Boucher et al, 2015; Huiart et al., 2011; Pellegrini et al., 2010). Tackling this begins with understanding patients' perspectives and the challenges they face with adherence to the medication. This can be

explained by the patient's decision not to take prescribed treatment, which is likely influenced by their beliefs and views about medicines and their potential side effects (Horne and Weinman 1999).

Clinicians often anticipate that cancer patients will take their medication as recommended, and in circumstances when medication adherence is discussed, believe the patient when they say they are taking their medication as prescribed (Partridge et al. 2002). However, recent studies have highlighted that adherence is still a challenging issue with patients (Hess et al. 2017; Hirao et al. 2017). Adherence rates to oral chemotherapy medicines have been reported to range widely from 16% to 100% (Ruddy et al. 2009; Foulon et al. 2011; Verbrugghe, Timmers, Boons, Van Den Bemt, et al. 2016). According to Foulon et al. (2011), variations in adherence rates can be explained by the type of oral chemotherapy drug used (e.g., side effect profile, complexity of regimen), differences in the definition of adherence being applied in studies, and differences in the adherence measurement methods that are used.

This review aims to understand what is known about the factors that influence adherence to oral chemotherapy medicines among CRC patients. Ageing populations, sociodemographic variations, gender-related health behaviours, and the advanced stage at which patients are diagnosed are some of the factors discussed in the previous chapter that contribute to the rise in CRC incidence and mortality rates. Oral chemotherapy treatment options such as capecitabine and trifluridine-tipiracil have made home-based CRC treatment more convenient, and they are also recommended as an adjuvant

treatment option for advanced CRC. However, the benefits of oral chemotherapy agents are contingent on CRC patients' adherence to treatment.

The severity of CRC treatment-related toxicities remains a prominent concern despite the oral chemotherapy agents' known safety and efficacy profiles (Van Cutsem et al. 2001; Hoff et al. 2001; Mayer et al. 2015). Therefore, it is important to determine whether CRC patients adhere to their treatment regimen, as adherence support could be a crucial element in reducing disparities in health outcomes. Improving CRC patients' adherence has the potential to not only enhance their quality of life but also decrease the progression of the disease and increase the overall survival rate of patients. Establishing a deeper understanding of the factors that influence oral chemotherapy medication adherence would therefore be beneficial to CRC care practises, potentially allowing for the development of interventions and strategies that could lead to improved drug use. This literature review aims to explore: (1) the measures used to assess adherence and (2) the known factors influencing adherence to oral chemotherapy medicines among colorectal cancer patients.

2.3 Methods

2.3.1 Search Strategy

CINAHL (Ebsco host), Medline (Ovid), Embase (Ovid), Ovid Emcare, Assia, PsychInfo (Ovid), and the Cochrane Database of Systematic Reviews were used to conduct literature searches. Articles were screened from 2001 onwards to correspond with the approval of the first oral chemotherapy drug (capecitabine, Xeloda®) for use in colorectal cancer patients by the

Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. As seen in *Table 2.1*, the search strategy included a combination of MeSH terms. Literature searches were undertaken, linking the MeSH terms '*oral*', '*chemotherapy*', '*colorectal*' and '*adherence*'. Searches were limited to articles in which adherence was one of the primary purposes of the research, and study abstracts were an invaluable resource for determining whether this criterion was met. Article references were combed through to find related articles, and subsequently added to the reference database tool. This was helpful in locating additional articles that had not been found in the database search. For the purpose of this review, all types of research designs (e.g., quantitative, and qualitative) were sought. Research protocols, on the other hand, were excluded.

While a thorough search of electronic databases was carried out using specific search terms and inclusion criteria, this analysis was not intended to represent a systematic review. This literature review seeks to examine the available evidence relating to colorectal cancer patients and the factors influencing adherence to oral chemotherapy treatment.

Table 2.1 Search Strategy with MeSH terms

MeSH Terms	Oral, Administration Oral Drug Administration Oral Chemotherapy "Oral Chemotherapy" Capecitabine Lonsurf Trifluridine and Tipiracil Tablet* Oral medication	AND	Antineoplastic agents, Combined Chemotherapy, Cancer Chemotherap* Cancer Chemotherap* Antineoplastic Antineoplastic agent* Antineoplastic drug* Anti-cancer drug* Anticancer Anticancer drug* Cancer therap* Cancer treatment*	AND	Colorectal Neoplasms Colorectal cancer Bowel cancer Rectal cancer	AND	Patient Compliance Medication Compliance Medication Adherence Adherence "Medication adherence" nonadherence or non-adherence noncompliance or non-compliance patient concordance or "patient concordance" patient cooperation non-adherent patient* or nonadherent patient* non-compliant patient* or non-compliant patient* over-adherence or overadherence
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2.3.2 Study Selection

Studies were included in the review according to the criteria outlined below:

- Adults aged 18 years old or older. There was no restriction on gender type, height, or weight.
- Patients treated for colorectal cancer and/or gastrointestinal cancer, as this refers to malignant conditions of the gastrointestinal tract (GI tract) and accessory organs of digestion, including the colon and rectum. Only studies that specifically identified colorectal cancer patients were included. All studies that did not refer to these patient groups were excluded from the review.

- Patients receiving oral chemotherapy medication as a single agent or as adjuvant treatment were included.
- Studies that have taken place in a primary or secondary care setting were included. There was no restriction on the location or country in which the study was conducted.
- Articles published in the English language.

2.3.3 Assessment of Risk of Bias

The possible risk of bias of included studies was assessed using the National Institute for Health and Clinical Excellence (NICE) guidelines preferred appraisal checklist (NICE 2018). The checklist consists of six areas to consider when evaluating validity and bias and includes: participation, attrition, prognostic factor measurement, confounding measurement, outcome measures, and analysis and reporting. The purpose of this appraisal was to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct, and analysis. Only if the participants were not informed beforehand and adherence was assessed using a medication event monitoring system (MEMS) or a direct test, such as blood samples, was the measurement of adherence considered without bias. This is because MEMS are considered the gold standard for measuring adherence, whereas direct methods determine the amount of metabolites in the blood (Osterberg et al 2005). All papers selected for inclusion were subjected to rigorous appraisal, and any disagreements were discussed with two supervisory reviewers until a consensus was reached. Each question was answered 'yes' or 'no' and if there was insufficient detail reported in the study, it was marked as unclear (presented in *Table 2.2*).

Figure 2.1 Flow diagram illustrating search strategy (Moher et al. 2009). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Chart.

Adherence to Oral Chemotherapy medication

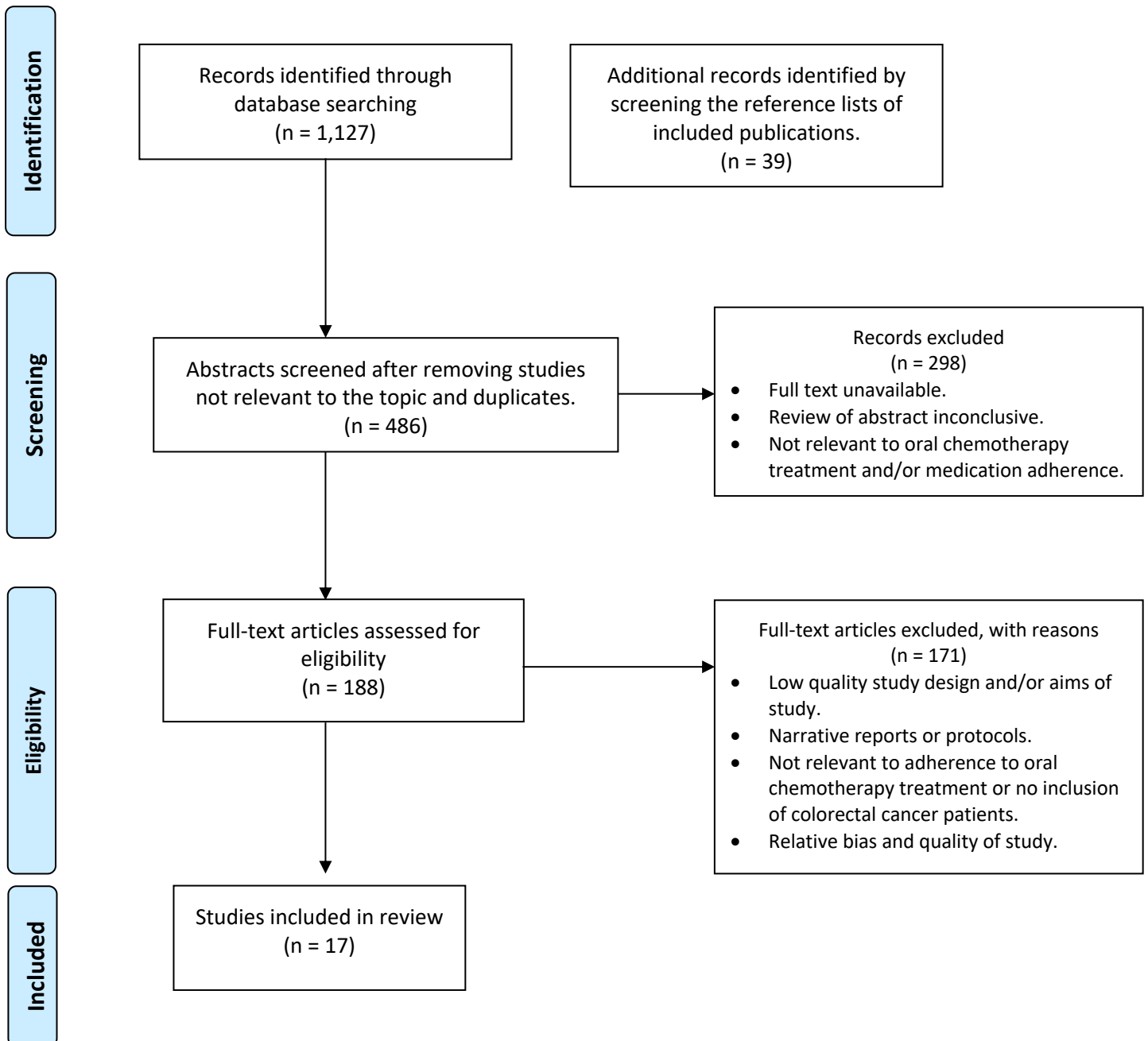


Table 2.2 – Risk of Bias.

Study	Participation	Attrition	Factor Measurement	Outcome Measurement	Confounders	Statistical Analysis
Krolop L et al (2013)	+	+	?	+	+	+
Le Saux et al (2018)	+	+	-	+	+	+
Walter T et al (2014)	+	+	-	+	+	+
Timmers L et al (2016)	+	?	+	+	?	+
Bourmaud A et al (2015)	+	+	?	?	+	+
Simons S et al (2010)	+	+	-	?	+	+
Bhattacharya D et al (2012)	+	?	+	?	-	+
Kawakami K et al (2017)	+	+	-	?	?	+
Schneider SM et al (2014)	+	-	+	?	+	-
Chen Y et al (2020)	+	?	+	?	-	-
Hirao et al (2017)	+	-	?	?	+	-
Fernandez-Ribeiro F et al (2016)	+	+	?	?	-	-
Sugita K et al (2016)	?	?	+	?	-	+
Kovacic L et al (2017)	+	?	?	?	?	-
Patel A et al (2018)	+	-	?	?	-	?
Winterhalder et al (2011)	+	-	-	?	-	-
Figueiredo Junior AD et al (2014)	+	-	-	?	-	-

(+ = Yes, - = No, ? = Unclear, N/A= Not Applicable).

*Participation – source of target population, recruitment, inclusion and exclusion criteria, adequate study participation, baseline characteristics.

*Attrition – attempts to collect information on participants who dropped out, reasons for loss to follow-up provided.

*Factor measurement – definition of factor, valid and reliable measurement, method and setting, proportion of data available for analysis.

*Outcome measurement – definition of outcome, valid and reliable measurement of outcome.

*Confounders – important confounders measured, valid and reliable measurement of confounders.

*Statistical Analysis – presentation of analytical strategy, reporting of results.

Table 2.3: Study characteristics on adherence influencing factors to oral chemotherapy medicines.

Author/ Country	Adherence Measures	Sample size and Results	Determinants of non-adherence (+ or -)	Conclusion of study
Chen Y et al (2020) China	Indirect: self-report questionnaire	(n=132) Self-developed adherence scale adapted from literature. 50%, 47.7% and 40.8% showed good adherence in early, middle and late stages of chemotherapy. 28.6% had good overall compliance. 71.4% had poor overall adherence.	Forgetting and side effects two main reasons for non-adherence. Living with family, job status during chemotherapy and perceived benefits.	<ul style="list-style-type: none"> Adherence could be improved by interventions related to family, work and patient's perception of oral chemotherapy. Overall adherence was poor, especially in last stages of chemotherapy, and adherence showed a downward trend during chemotherapy.
Le Saux et al (2018) France	Direct : plasma concentration Indirect : (1) self-report questionnaire (2) Pill Count (3) microelectronic monitoring system (MEMS)	(n=40) Measurement of the level of fluoro-beta-alanine (FBAL-metabolite of capecitabine) in the plasma. 'Dose taking' measured through medication possession ratio (MPR) and 'dose-timing' measured through electronic monitoring device (MEMS). For pill count - mean adherence in the 2nd phase (n=20) was 98.42% and median (n=40) was 100% - 95%. Mean MPR adherence 96.17%.	Patients taking extra doses in a day; skipping a day of dosing and 'compensating' by taking extra doses the following day.	<ul style="list-style-type: none"> Adherence was excellent suggesting over-adherence and potential safety implications for outpatient drugs.
Patel A et al (2018) USA	Indirect: Prescription Refill data	(n = 1630) MPR of $\geq 80\%$ was 84.5% and MPR of $\geq 90\%$ was 71.2%. Mean MPR was 91%. The mean PDC at 3 months was 81%.	Nausea and vomiting; abdominal pain; neutropenia; ileus, diarrhoea and missed doses.	<ul style="list-style-type: none"> Further research is needed to assess the clinical and economic implications of better adherence and persistence for metastatic CRC taking Trifluridine/Tipiracil.
Kawakami K (2017) Japan	Indirect: Patient-reported treatment diaries	(n=282) Rate defined as number of patient intakes per 28 scheduled intakes in one cycle. The ratio of patients who completed capecitabine treatment on XELOX was 83.6%. Median adherence rate in the 1st cycle was 94.0%. 16.4% showed non-adherence.	Nausea and vomiting; diarrhoea; missed doses; pain; peripheral neuropathy; fever.	<ul style="list-style-type: none"> Considerable number of patients (16.4%) showed non-adherence, main reasons was side-effects. High adherence may be explained by patient state (e.g. kidney function etc.) better under an adjuvant therapy setting.
Hirao et. Al (2017) Japan	Indirect : Prescription Refill data	(n=117) Adherence defined in terms of percentage of oral chemotherapy medications taken through patients' last hospital visit to the latest visit. 56.4% classified as good adherence. No patients showed a discrepancy between the numbers of medication prescribed in medical records vs. questionnaire.	Diminished sense of priority for medication, employed, treatment related factors (diarrhoea, dosage regimen, patient-caused treatment interruptions due to worsening of symptoms).	<ul style="list-style-type: none"> History of patient-caused treatment interruptions due to worsening symptoms associated with non-adherence. Identifying gastrointestinal cancer patients through periodic screening and connecting them with appropriate education and support improves adherence.
Kovacic L et al (2017)	Indirect: Prescription refill data	(n=894) Primary adherence measure was the number of potential altered treatment date incidents (ATDI) by	Clinical delay; patient scheduling issues; patient non-adherence; no identifiable reason; patient choice of delay.	<ul style="list-style-type: none"> The reasons for altered treatment date incident not identified in 52.2% of prescriptions. Risk of overestimation of adherence.

Canada		comparing the predicted vs. actual refill dates. Adherence rate of 90% (after exclusions) 45.2% associated with an altered treatment date incident based on initial algorithm. Reduced to 29.5% after adjusting for clinic scheduling processes and 10.2% after manual chart review to adjust for valid reasons for delay.		
Sugita K et al (2016) Japan	Indirect: Patient-reported treatment diaries	(n=50) Rate defined as the number of patient intakes per 20 scheduled intakes in one cycle. Adherence rate 95% in the 1 st cycle; 97% in the 2 nd cycle, maintained to 98% in the 3 rd and 4 th cycles.	Nausea and vomiting; decreased appetite; abdominal pain; neutropenia or ileus; fever; forgetfulness.	<ul style="list-style-type: none"> • Patient guidance by outpatient clinicians is important, potentially lead to improved adherence. • Reduced adherence linked to high ratio of nausea and vomiting and side-effects. Management of symptom of cancer-related pain important.
Timmers L et al (2016) Netherlands	Direct: Plasma concentration Indirect: (1) self-report questionnaire (2) Pill count	(n=92) Measurement of plasma concentration was observed. There was an absence of any metabolite in 3 of 160 (1.9%). 91% (n=84) had a rate of ≥ 95 and $\leq 105\%$. The % of pts reporting non-adherence for MARS 16% in cycle 1, 23% in C3, and 29% at C5. For pill count - AR was 99.3 and 100% respectively. Most had an AR $>95 < 105\%$. Only 9% had an AR < 95 or > 105 .	Forgetfulness; fatigue; flatulence; nausea and vomiting; muscular pain; loss of appetite; dry mouth.	<ul style="list-style-type: none"> • Adherence measure with MARS decreased over time thus management implementation in long term treatment required. • Adverse event management important to support persistence.
Fernández-Ribeiro F et al (2017) Spain	Indirect: (1) self-report questionnaire (2) Pill count	(n=111) AR 78.4% (81.7% in the initiation sub-group vs 72.5% in the continuation sub-group).	Fatigue; muscular pain, side-effects (diarrhoea), treatment modification, disease evolution.	<ul style="list-style-type: none"> • A correlation was observed between quality of life and adherence. Higher QOL score showed superior adherence levels. • Development of toxicities and the alteration of QOL can lead to reduction in adherence.
Bourmaud A et al (2015) France	Indirect: MEMS	(n=20) 23 missed doses in 2,272 predicted doses (99% adherence). 10% (n=2) less adherent, 20% (n=4) highly adherent and 70% (n=14) adequately adherent.	Irregular, active life, with family and professional obligations less adherent; highly educated; side effects and management of symptoms.	<ul style="list-style-type: none"> • Educational programs tailored to patient profiles should be evaluated to enhance adherence. • Tendency for lower adherence observed among more highly educated patients with an irregular, active life.
Schneider SM et al (2014) USA	Indirect: (1) self-report questionnaire (2) Prescription refill data.	(n=45) AR measured clinical records at 2 and 4 months. For self-reports adherence was 86% and 89% over 2 & 4 months. Prescription refill - the percentage who had adequate supply to take medicine was 73.3% at 2 months and 71% at 4 months.	System barriers (late pharmacy deliveries, ordering of incompatible medications, unclear instructions when to start oral agents).	<ul style="list-style-type: none"> • Self-reports rates were greater than those indicated by pharmacy refill rates. Positive correlation with relationship of nurse with patients.

Figueiredo Junior AD et al (2014) Switzerland	Indirect: Pill count	(n= 30) Rate defined number of leftover medicines that had been given out at the start of each new cycle. AR was 88-96%. 88.3% for metastatic colon cancer; 90.4% for non-metastatic colon cancer and 94.3% for rectal cancer.	Dyspnoea; fatigue; anxiety; worsening financial difficulties.	<ul style="list-style-type: none"> Health professionals need a greater focus in the monitoring of patients taking oral treatment regimen, Patients with lesser degrees of dyspnoea had greater compliance.
Walter T et al (2014) Canada	Indirect: (1) Self-report questionnaire (2) Pill count (3) MEMS	(n=19) Patient were considered adherent if the 3 measures suggested 80% or greater doses taken. The AR for SR was 100% (86-100%), for PC overall AR was 100%. For MEMS overall AR was 61% if all dosing errors are considered.	Missed doses; dosing interval error.	<ul style="list-style-type: none"> Adherence of people with cancer may be higher than chronic disease because patients are 'highly motivated' and have 'too much to lose'. Did not identify a major adherence issue with Capecitabine adherence.
Krolop L et al (2013) - Germany	Indirect: MEMS	(n= 73) Adherence was >=90% and non-adherence <90%. Patients instructed only to open container when they are taking capecitabine. Pts also given modular medication management by pharmacist. AR ranged between 98.2% and 100.5% in initially adherent patients and between 93.8% and 102.7% in initially non-adherent pts.	Difficulties swallowing, nausea and vomiting, forgetfulness, hand-foot syndrome, toxicity with co-medication.	<ul style="list-style-type: none"> An early adherence screening effectively distinguishes between adhering and non-adhering to capecitabine. Specific adherence support associated with increased adherence of initially non-adherent patients.
Bhattacharya D et al (2012) United Kingdom	Indirect: Self-report questionnaires.	(n=43) The MARS ranges from 5-25. Adherence (MARS=25) and non-adherence (MARS<25). Non-adherence reported by 23.3% (n=10) of whom 4 reported multiple reported multiple methods of deviation.	Forgetfulness, Medication compliance; missed doses; side-effects (diarrhoea, swallowing, nausea); difficulties with blister packs.	<ul style="list-style-type: none"> Concerns expressed by patients with the management of side effects. Development for healthcare professionals to carry out more comprehensive medical histories. Mindful of concerns and offer targeted counselling and treatment plans.
Winterhalder et al (2011) Switzerland	Indirect: Patient self-reported treatment diaries	(n=177) AR was 91% (n=161) fully compliant while 9% (n=16) reported compliance error. The compliance rate among pts with no reported a/e was 95%, but among pts with >3 a/e the compliance was 66.7%.	Forgetting to take treatment; misunderstanding instructions; diarrhoea; hand-foot syndrome; nausea and vomiting.	<ul style="list-style-type: none"> Self-reported compliance with Capecitabine treatment is high and seems adversely affected by side-effects. Limitations with the method used to measure adherence.
Simons S et al (2011) Germany	Indirect: MEMS	(n=24 colorectal and breast; 24 intervention group) Mean overall adherence higher in intervention group (97.9% vs 90.5%); mean daily adherence significantly higher (96.8% vs 87.2%, p = 0.029).	Severe toxicity; forgetfulness.	<ul style="list-style-type: none"> Development of an adherence monitoring and enhancing infrastructure is a necessary prerequisite to exploit full potential if oral chemotherapy medication. Screening systems to detect potential non-adherers would support the rational utilization of required resources.

2.4 Results

2.4.1 Literature Search

A flow chart of the search strategy is presented in *figure 2.1*. A total of 1166 titles were found in the literature search, with additional articles identified through the reference list of studies that met the inclusion criteria. After screening the records and removing all duplicates and titles that were not deemed relevant, the abstracts were reviewed for any mention of adherence to oral chemotherapy treatment among colorectal or gastrointestinal patients. Studies whose full text was unavailable or had no relevance to oral chemotherapy medicine were removed from those records. Following that, a total of 188 full-text papers were assessed to see if they satisfied the eligibility requirements. The reasons for article exclusion included studies that were irrelevant to oral chemotherapy treatment among colorectal or gastrointestinal cancer patients, as well as studies that included gastrointestinal patients but did not report a breakdown of the different cancer groups, making it unclear whether colorectal cancer patients were assessed in the study. The review included 17 studies based on the assessment of full-text articles.

2.4.2 Risk of Bias

Table 2.2 presents the risk of bias evaluation for each study. The included studies had a moderate risk of bias overall. Both the factor and outcome measurement were largely measured with an instrument whose validity was unknown. As a result, the possibility of bias in relation to the respective assessment questions on factors

measurements and adherence was mostly graded as unclear. The limitations are highlighted in *section 2.6*.

2.4.3 Study Characteristics

The main study characteristics of the 17 articles are summarised in *Table 2.3*. The study characteristics from the included studies were extracted and assembled into a standardised table. The extracted data included the following: the author's name; the country of origin of the study; the year of publication; the method of adherence used and how adherence was measured, including the sample size used; details of the adherence results; determinants that affected (non)-adherence; and the conclusion of the study.

The studies ranged from a variety of continents, including nine in Europe (Switzerland, Netherlands, United Kingdom, Germany, France, and Spain); four in Asia (China and Japan); and four in North America (USA and Canada). The sample size for the studies ranged widely between 19 and 1630 patients. Colorectal cancer patients were included in all of the research, but only four studies focused exclusively on this cancer type (Chen Y et al 2020; Sugita et al. 2016; Kawakami et al. 2017; Patel et al. 2018). Capecitabine (Xeloda®) was the most commonly used oral chemotherapy medicine in 15 studies, followed by Trifluridine-Tipiracil Hydrochloride (TFTD) in two studies.

2.4.4 Methods used for assessing adherence to oral chemotherapy medicines

Table 2.4 Direct and Indirect Methods

Methods	Studies
Direct Methods	
Measurement of biological markers in blood (n=1)	Le Saux et al. 2018
Metabolite Level in Plasma (n=1)	Timmers et al. 2016
Indirect Methods	
Self-report questionnaire surveys (n=8)	Bhattacharya et al. 2012; Schneider et al. 2014; Walter et al. 2014; Timmers et al. 2016; Fernández-Ribeiro et al. 2017; Hirao et al. 2017; Le Saux et al. 2018; Chen et al. 2020.
Self-report treatment diaries (n=3)	Winterhalder et al. 2011; Sugita et al. 2016; Kawakami et al. 2017
Prescription refill data (n=4)	Schneider et al. 2014; Hirao et al. 2017; Kovacic et al. 2017; Patel et al. 2018
Pill Counts (n=5)	Figueiredo Junior et al. 2014; Walter et al. 2014; Timmers et al. 2016; Fernández-Ribeiro et al. 2017; Le Saux et al. 2018
Medication Electronic Monitoring System (MEMS) (n=5)	Simons et al. 2011; Krolop et al. 2013; Walter et al. 2014; Bourmaud et al. 2015; Le Saux et al. 2018

As illustrated in Table 2.4, the measurement of adherence varied across the studies, e.g., plasma metabolite level, self-report methods, prescription refill data, pill counts, and electronic monitoring system. The methods used to measure adherence are described below, from direct and indirect methods.

- Measurement of biological markers in blood: In one study, biological tumour markers were analysed, and the clinical benefit rate was defined as the proportion of capecitabine-treated patients who obtained a complete response, a partial response, or stable illness (Le Saux et al. 2018). After 3 and 6 cycles, the tumour response was examined based on marker levels. The evaluation of tumour response in 35 patients revealed that 23% had a partial response, 54% had stable disease, and 23% had disease progression.

- Metabolite Level in Plasma: One study measured the level of metabolites in the plasma (Timmers et al. 2016). The study found that 3 out of 160 patients who reported taking capecitabine 20 minutes to 12 hours before their blood was taken did not have any metabolites.
- Self-report questionnaire surveys: Eight studies employed self-report questionnaire surveys (Bhattacharya et al. 2012; Schneider et al. 2014a; Walter et al. 2014; Timmers et al. 2016; Fernández-Ribeiro et al. 2017; Hirao et al. 2017; Le Saux et al. 2018; Chen et al. 2020). Using self-report surveys, the medication adherence rate ranged from 71% to 84%. In the study by Timmers et al. (2016), adherence was measured at cycles 1, 3, and 5, and the number of patients reporting non-adherence increased over time from 16% in cycle 1 to 29% at cycle 5. There were similar results in the Fernández-Ribeiro et al. (2017) study, where the adherence rate was higher in the initiation group compared with the continuation subgroup (81.7% vs. 72.5%).
- Self-report treatment diaries: Three studies used self-reported treatment diaries (Winterhalder et al. 2011; Sugita et al. 2016b; Kawakami et al. 2017). In these studies, the adherence rate was defined as taking all recommended doses for the duration of the treatment. Compliance errors were defined as any intake errors or incidences that resulted in non-adherence. The adherence rate observed with the use of diaries in these studies ranged from 83.6% to 100%.
- Prescription refill data: Four studies used prescription refill data to calculate adherence as the percentage of oral chemotherapy medication taken from the prescribed date from the last visit to the latest visit, i.e., the proportion of days covered (Schneider et al. 2014; Hirao et al. 2017; Patel et al. 2018). In general, the

adherence rates for prescription refill data were lower than other indirect methods, ranging from 56.4% to 90%. In the Kovacic et al. (2017) study, the primary measure of adherence was the number of altered treatment incidents by comparing the predicted refill dates against the actual refill dates.

- Pill counts: were used in five studies to measure adherence, whereby patients were provided with a precise number of pills at the start of each cycle and the number of returned pills was used to calculate the number of missed doses (Figueiredo Junior et al. 2014; Walter et al. 2014; Timmers et al. 2016; Fernández-Ribeiro et al. 2017; Le Saux et al. 2018). The adherence rates for the studies measured with a pill count were high overall, ranging from 88% to 100%. Pill counts require patients to return containers, and in the Walter et al. (2014) study, pill counts were performed on 15 patients (cycles 1, 2, and 16), and on six occasions, patients failed to bring their pill containers to visits despite reminders.
- Medication electronic monitoring system (MEMS): this method was used in five of the studies (Simons et al. 2011; Krolop et al. 2013; Walter et al. 2014; Bourmaud et al. 2015; Le Saux et al. 2018). Adherence rates for studies using MEMS were considered high, ranging from 90.5% to 102.7%. Adherence was measured during treatment intake using the timing of each opening of the bottle with MEMS caps. The MEMS caps were then analysed using the uploaded data, and overall adherence was calculated by dividing the number of actual openings recorded by the MEMS by the number of expected openings. Only two studies (Simons et al. 2011; Bourmaud et al. 2015) informed patients that adherence was being monitored for ethical purposes and asked them to only open the containers when taking their dose. In the Bourmaud et al. (2015) study, poor adherence was defined

as having an opening time variability of more than one hour and good adherence

as having an opening time variability of less than 15 minutes.

2.4.5 Factors influencing adherence to oral chemotherapy treatment

Table 2.5 lists the determinants along with supporting evidence from the studies that have an influence on CRC patients' adherence to oral chemotherapy agents. The findings are structured according to the five categories provided by the WHO framework (WHO, 2003) to outline the diverse range of factors that influence medication adherence.

Table 2.5 Factors influencing CRC patients' adherence to oral chemotherapy agents

Determinants of Adherence Influencing Factors	Studies
Patient-related Factors	
Forgetting to take a dose	(Simons et al. 2011; Winterhalder et al. 2011; Bhattacharya et al. 2012; Krolop et al. 2013; Timmers et al. 2016; Chen et al. 2020)
Motivated patients' / high tolerability	(Bourmaud et al. 2015; Le Saux et al. 2018)
Perceiving greater benefits/ high expectations	(Bourmaud et al. 2015; Chen et al. 2020)
High treatment necessity	Bhattacharya et al. 2012
Negative beliefs about medication	(Krolop et al. 2013)
Diminished sense of priority	(Hirao et al. 2017)
Therapy-related factors	
Side effects/greater toxicity/ worsening of symptoms/ reduced level of symptoms	(Simons et al. 2011; Winterhalder et al. 2011; Bhattacharya et al. 2012b; Krolop et al. 2013; Figueiredo Junior and Forones 2014; Schneider et al. 2014a; Walter et al. 2014; Bourmaud et al. 2015; Sugita et al. 2016a; Timmers et al. 2016; Fernández-Ribeiro et al. 2017a; Hirao et al. 2017a; Kawakami et al. 2017; Kovacic et al. 2017; Patel et al. 2018; Le Saux et al. 2018a; Chen et al. 2020)
Discontinuation of treatment	(Timmers et al. 2016; Kovacic et al. 2017; Le Saux et al. 2018)
Dose adjustments	(Timmers et al. 2016; Hirao et al. 2017; Le Saux et al. 2018)
Longer duration of treatment	(Timmers et al. 2016)
Swallowing tablets	(Bhattacharya et al. 2012; Krolop et al. 2013)
Healthcare system-related factors	
Late medication deliveries	(Schneider et al. 2014)
Receiving unclear directions when starting treatment	(Schneider et al. 2014)
Unavailable medical service	(Schneider et al. 2014)

Socioeconomic related factors	
Gender (male)	(Timmers et al. 2016)
Age (low, old and/or retired)	(Bourmaud et al. 2015; Kawakami et al. 2017)
Education status (low)	(Bourmaud et al. 2015)
Living alone	(Kawakami et al. 2017)
Family support (living with parents)	(Chen et al. 2020)
Employment status	(Bourmaud et al. 2015; Chen et al. 2020)
Higher quality of life	(Fernández-Ribeiro et al. 2017a)
Attending social events	(Chen et al. 2020)
Condition-related factors	
Number of co-medications	(Timmers et al. 2016)
Severity of the disease	(Le Saux et al. 2018b).
Contraindicated medication	(Schneider et al. 2014)

Patient-related factors

Six of the included studies identified forgetfulness as the most prevalent patient-related reason for non-adherence. Chen et al. (2020) discovered that in the middle and late stages of chemotherapy, 92.9% and 80% of patients', respectively, failed to take their oral chemotherapy medication on time due to forgetfulness. Additionally, 16.3% of patients who had forgotten to take their dose cited remembering the time of day as the main barrier to adherence (Bhattacharya et al. 2012). Furthermore, a history of patient-caused interruptions was closely related to non-adherence, primarily due to worsening symptoms and a lower perception of drug importance (Hirao et al. 2017). Krolop et al. (2013) found that nonadherence occurred in patients who were opposed to taking medicines or who compensated for earlier non-adherence during treatment breaks.

According to Fernández-Ribeiro et al. (2017), the difference in adherence rates may be because patients were more motivated at the start of treatment because they had just been given a new diagnosis and seemed more open to hearing and reading information. Bourmaud et al. (2015) discovered that in motivated patients, 34.2%

were likely to find out more information about their medicines, and 68.4% were likely to organise their daily lives around their dosing regimen. Furthermore, interviews conducted by sociologists to evaluate patient adherence profiles revealed that patients had high expectations about the efficacy of the Capecitabine treatment. As a result, patients were willing to endure side-effects so long as they did not interfere with their treatment. Chen et al.'s (2020) study utilised a culturally adapted Chinese version of the health belief model, and the analysis revealed that patients who perceived greater benefits from the oral chemotherapy medication were more likely to exhibit high levels of adherence.

Therapy-related Factors

Side effects of the oral chemotherapy medicines were reported in all studies and were one of the main reasons for non-adherence. In a study identifying adherence profiles, the main issue reported by all patients was the occurrence of side effects and the management of symptoms, with over two-thirds of patients (62.5%) suffering from quite severe effects (Bourmaud et al. 2015). In an observational study with patients receiving capecitabine, the majority of the side effects described by patients had reduced in duration and intensity except for the tingling, muscular pain, fatigue, and diarrhoea that were the most frequent and had an influence on the quality of life (Fernández-Ribeiro et al. 2017). Diarrhoea was closely associated with non-adherence in three studies, and can result in severe dehydration and physical deterioration if left untreated (Winterhalder et al. 2011; Bhattacharya et al. 2012; Hirao et al. 2017). In addition, in an observational cohort study, intentional nonadherence was seen in

patients with difficulties swallowing tablets due to nausea and emesis caused by Capecitabine. (Krolop et al. 2013). This was also reported in another study, though it also found that these difficulties with swallowing were not reported to the healthcare team (Bhattacharya et al. 2012).

The most frequently reported toxicities of the treatment were gastrointestinal problems (diarrhoea, nausea, and vomiting), hand-foot syndrome (HFS), fatigue, mouth sores, and abdominal pain. Treatment-related toxicities such as HFS caused serious discomfort to patients and were the reason for dose adjustments discontinuation of therapy, which influenced adherence (Timmers et al. 2016; Le Saux et al. 2018b). In the Timmers et al. study (2016), one third of patients discontinued their treatment before finishing 5 cycles, stating that side effects were a reason for discontinuation. Also, the study found that almost two-thirds of patients experienced at least one dose adjustment to their oral chemotherapy medicine made by their healthcare provider. The most common adjustments made were reducing the dose for the next cycle of treatment or delaying when the patient restarted. The authors reasoned that experiencing side effects may decrease quality of life and as a result, influence their decisions to skip or reduce doses. Some cancer patients, however, chose to withdraw from treatment as a means of coping with worsening side effects and reduced levels of symptoms (Hirao et al. 2017). The study found that the likelihood of intentional non-adherence increased over the length of treatment, for example, by adjusting the dose or deciding to skip a dose.

In a study examining the impact of an intensified multidisciplinary pharmaceutical care programme on the adherence of cancer patients taking capecitabine, it was reported that nine patients in the control group discontinued therapy due to severe toxicity, while only two patients in the intervention group discontinued treatment (Simons et al. 2011). The care program for the intervention group consisted of a combination of written and spoken information provided by two pharmacists, including specifics on their treatment and the importance of high adherence to the medication. Patients who were well informed and knew what to expect during treatment were better prepared to manage side effects and the onset of symptoms, thus reducing the risk of patient withdrawal.

Healthcare system-related factors

In the study by Chen et al. (2020), 12% of patients missed a dose because the medical service was unavailable during the final phase of chemotherapy treatment. In addition, in a study using a nurse tailored intervention approach, system barriers interfered with adherence in around 10% of patients (Schneider et al. 2014). These barriers had a minimal bearing on the medication-taking behaviour of patients. Examples of the barriers include late medication deliveries, medications ordered that are contraindicated with oral chemotherapy medications, and receiving unclear directions when starting the treatment.

Socioeconomic related factors

In a study that combined adherence with a sociological approach during patient interviews, it was discovered that older or retired patients with lower educational backgrounds and no professional or family commitments were more likely to adhere to their medication than highly educated patients with family responsibilities (Bourmaud et al. 2015). This was due to the 'fear of forgetting a dose' and following directions strictly, in contrast to patients with higher education levels, who were more likely to be aware that they could miss a dose. Chen et al.'s (2020) study found that factors influencing adherence included living with one's parents, occupational status during chemotherapy, and the perceived benefits of treatment. It was reported that patients who lived with their parents and/or attended social events had a poorer adherence response, especially in the middle stage of chemotherapy, which may be because the majority of those who lived with their parents were young people. Also, patients who worked a part-time job performed better with adherence than those who did not work.

Moreover, Fernandez-Ribeiro et al. (2017) discovered a correlation between patients with high QOL scores and high adherence rates. The SF-12 test was used to assess QOL, and patients were asked whether their work or daily activities were limited. In another study, cancer status had little effect on adherence, but patients' success status and living alone status were linked to adherence (Kawakami et al. 2017). Also, three included studies (Winterhalder et al. 2011; Krolop et al. 2013; Schneider et al.

2014) found no significant correlation between adherence and sociodemographic factors such as age and gender.

Condition-related factors

In a study about the potential safety and clinical implications of over-adherence to capecitabine in colorectal cancer patients, it was found that metastatic patients may over-adhere to their oral medicines because they realise they have a serious condition and are therefore inclined to take more (Le Saux et al. 2018). Also, Timmers et al. (2016) observed that a variety of variables, including the number of prescribed medications, were positively associated with the incidence of receiving a dose adjustment.

2.5 Discussion

This review aimed to determine the measures used to assess adherence and the known factors that influence CRC patients' adherence to oral chemotherapy medicines. Across the studies, there were variations in the methods used to assess adherence, how it was defined, and the criterion for when a patient was considered adherent to their medication. This review suggests that adherence to oral chemotherapy treatment in this patient group is multi-factorial. There is evidence to support each of the five WHO groups of factors that influence adherence, as shown in Table 2.5.

There were variations in the methods used to assess adherence to oral chemotherapy agents. In two studies (Timmers et al. 2016; Le Saux et al. 2018), direct approaches that are an objective measure of adherence were used by either measuring the biological marker or assessing the level of drug metabolites in the plasma were used. Previous studies have also used direct approaches to measure adherence using urinary drug metabolites and biomarkers (Özdemir and Endrenyi 2019; Kotsis et al. 2021). While direct methods are considered the most reliable and provide strong evidence of the ingestion of the drug, there is no gold standard for measuring adherence (Osterberg, Lars; Blaschke 2005). This method does not provide any additional details on patterns, levels of adherence, or any influencing factors (Lam and Fresco 2015). Furthermore, because the drug pharmacokinetics can be highly variable, they only accurately reflect short-term adherence and can overestimate patients' long-term adherence (Van Den Bemt et al. 2012). This is due to the fact that direct methods do not provide accurate timing of doses, and can be subject to manipulation (Ruddy et al. 2009). For example, after a CRC patient consumes an oral agent, it is metabolised and absorbed by the body. Extra doses of medication taken before a scheduled clinic may therefore distort the results for medicines with shorter half-lives.

All of the studies used indirect methods, with self-report questionnaire surveys being the most common. The medication adherence report scale (MARS-5) was used in two studies (Bhattacharya et al. 2012; Timmers et al. 2016) to assess adherence, which is a measure developed in the UK (Horne and Weinman 2002a). The MARS scale has demonstrated potential as a rigorous tool for measuring medication adherence across a range of chronic health conditions (breast cancer, rheumatoid arthritis, and chronic

obstructive pulmonary disorders) (Kim et al. 2014; Kumar et al. 2015; Fischer et al. 2018). The MARS comprises five items, four of which are related to intentional nonadherence, such as the likelihood to avoid, forget, adjust, and stop taking medication, whereas one MARS item focuses on forgetting medication (Chan et al. 2019). In addition, six studies made use of self-developed adherence scales based on related literature and publicly available scales. However, the scales' reliability and validity were not disclosed; therefore, caution should be taken when interpreting the results using modified tools.

The medication adherence rate varied between studies, ranging from 56.4% to 100%. The findings are consistent with other reviews of indirect measures in the literature (Mathes et al. 2014; Greer et al. 2016; Verbrugghe, Duprez, et al. 2016). The reasons for the variations are complex, but they can in part be attributed to the different methods for assessing medication adherence and the variations in follow-up times in studies where adherence is measured over many treatment cycles. The adherence rates for prescription refill data ranged from 56.4% to 90%, which was lower than other indirect methods. One explanation for this, according to Ruddy et al. (2009), is that refill data is less susceptible to the Hawthorne effect because patients are unaware when they take the medication that adherence will be assessed later. Furthermore, self-report measures have been shown to overestimate adherence (Waterhouse et al. 1993) because patients are aware that their medication adherence is being measured, which may impact their actual levels. Waterhouse et al.'s (1993) study compared self-reported adherence, pill count, and the use of MEMS in breast cancer patients to assess the adherence to tamoxifen. They noted that patient self-

report (98.6%) had a much higher rate of adherence than pill counts (92.1%) and MEMS (85.4%). Even though patient manipulation can affect MEMS results as they are aware of monitoring, it is still considered to be less susceptible to it and offers the most reliable indirect approach (El Alili et al. 2016). However, MEMS caps can be an expensive tool to implement in clinical settings and can measure adherence incorrectly. For example, opening the bottle without taking the medication or opening it once with double takeout may result in overestimation or underestimation of adherence.

Several influencing factors were identified as being associated with non-adherence among CRC patients taking oral chemotherapy agents. Forgetfulness was the most common patient-related factor. These findings are consistent with evidence from other chronic diseases such as breast cancer, rheumatoid arthritis, and chronic myeloid leukaemia (Grunfeld et al. 2004; Van Den Bemt et al. 2012; Kardas et al. 2013; Lea et al. 2018). A recent study by Muluneh et al. (2018) reported a number of demographic factors linked to forgetfulness, including being under 50 years old, taking oral chemotherapy medication for more than 6 months, and having a cancer diagnosis for more than a year. Younger and older ages were factors linked with lower adherence in CRC patients, according to three studies (Bourmaud et al. 2015; Kawakami et al. 2017; Chen et al. 2020). Although the reasons for non-adherence in this patient group remain unclear, there are several studies that have reported a correlation between younger and older age groups and poor adherence in other cancer groups (Partridge et al. 2003; Noens et al. 2009; Xu et al. 2012). Xu et al.'s

(2012) study suggests that younger men with breast cancer may be affected by their busy work schedules, side effects, or a perception of low benefits from taking tamoxifen. According to Molloy et al. (2009), patients with heart failure who believed their condition to be chronic were more likely to not take their medicine as prescribed. The mean age of these patients was 80 years. They may therefore perceive their illness differently than younger patients' do with respect to their timeline.

Medication adherence is not just a matter of taking medication but requires internal motivation for self-management, as reported in two studies (Bourmaud et al. 2015; Fernández-Ribeiro et al. 2017a). CRC patients who were motivated in these studies had high expectations about the treatment, were more determined at the start of treatment, were open to reading more information about their medicines, and were likely to make lifestyle changes that suited their dosing regimen. Conversely, two studies (Krolop et al. 2013; Hirao et al. 2017) reported a lower perception of drug importance as being closely related to non-adherence. There are a number of studies that have also reported a lower perceived necessity of oral chemotherapy medication and less self-efficacy in long term medication behaviour (Grunfeld et al. 2004; Noens et al. 2009; Jacob Arriola et al. 2014; Rosenberg et al. 2020).

Psychosocial factors of oral chemotherapy adherence are substantially influenced by cognitions (i.e., ideas, beliefs) and emotions (anxiety, fear, denial) regarding the oral chemotherapy drug and the severity of the disease (Kaptein et al. 2021). Jacobs et al. (2017) findings in patients' with diverse cancers underlined the importance of exploring illness perceptions and medication beliefs in efforts to motivate patients to

continue taking their oral chemotherapy treatment. Nonetheless, only three studies used behavioural tools such as the Beliefs about medicines questionnaire (BMQ) (Bhattacharya et al. 2012; Timmers et al. 2016) and the health belief model (Chen et al. 2020). Such health behaviour measures may help identify factors that explain and predict medication non-adherence among CRC patients, which is a relevant research priority. Beliefs about medication play an important role in an individual's medication adherence, and this has been substantiated in the WHO report (2003) and in previously published research (Horne and Weinman 1999; Horne, Sarah C E Chapman, et al. 2013). CRC patients may choose to continue therapy based on these beliefs if they believe the necessity or chances of success outweigh the treatment concerns.

Treatment-related side effects were the most common therapy-related causes linked to non-adherence in CRC patients. These findings are comparable with studies in other chronic conditions where drug-related symptoms were one of the factors leading to the discontinuation or dose adjustments of oral chemotherapy agents (Xu et al. 2012; Spoelstra et al. 2013; Greer et al. 2016; Verbrugghe et al. 2016; Muluneh et al. 2018). The findings suggest that minimising side effects is important for maintaining a good quality of life as well as reducing treatment-related toxicities and minimising treatment discontinuation. Molassiotis et al. (2009) tested the effectiveness of a symptom-focused homecare program in 164 patients with CRC and breast cancer treated with oral capecitabine. Patients were randomly assigned to receive either the nurse-led program or standard care for a period of 18 weeks. Weekly toxicity assessments were conducted, and the study discovered that the homecare program was positively related to a decrease in the severity of toxicity (oral mucositis,

diarrhoea, nausea, constipation, fatigue, and pain). In contrast to standard care, the homecare program was able to help patients manage the adverse effects. The timely management of side effects and for healthcare clinicians to check in with CRC patients regularly throughout the treatment period while educating them on the early recognition of signs and symptoms may improve their medication-taking behaviour.

Managing complex dosing regimens for pre-existing health conditions while receiving oral chemotherapy treatment can increase the illness burden in CRC patients. One study (Timmers et al. 2016) observed a positive association between the number of prescribed medications and the incidence of receiving a dose adjustment. Although the reasons were not clear from the literature, it is possible that nonadherence with comorbidity medication may exacerbate cancer-related symptoms such as fatigue, HFS, and diarrhoea. Antol et al.'s (2018) study on comorbidity medication adherence in various cancer patients found an association between the presence of cancer-related symptoms and low adherence to comorbidity medication. The identification of polypharmacy in patients with higher comorbidity levels, as noted by (Antol et al. 2018), may help facilitate medication adherence, as this can trigger referral resources, such as disease management, to ensure that adherence with medications for these comorbidities is not compromised during chemotherapy treatment.

An important consideration is whether socioeconomic status directly implicates cancer treatment adherence. There are several studies that have shown that all parts of the cancer treatment process can be influenced by socioeconomic status of a patient (Mastroianni et al. 2008; Cavalli-Björkman et al. 2011). According to one study,

older patients with lower educational backgrounds and no professional or family commitments were more likely to adhere to their medication than highly educated patients with family responsibilities (Bourmaud et al. 2015). This was in contrast to other research, which found that patients with a higher education or at least a secondary school education had better adherence behaviour (Noens et al. 2009; Timmers et al. 2014). Timmers et al. (2014) reported that patients on cyclic treatment, not living alone, and possessing a higher education level had a better chance of achieving optimal medication adherence. In addition, Cavalli-Björkman et al. (2012) explored whether patients' education levels and social networks influenced gastro-intestinal oncologists' decision making. According to the oncologists, patients' educational level and family structure, along with disease characteristics, had an influence when deciding which treatment to recommend for their patients. Oncologists spent more time responding to the queries and demands of patients with higher education or who had family support. Evidence, however, indicates that patients with lower socioeconomic status (i.e., education, income, and race) need extra support to understand medical information, which may lead to disparities in patient outcomes (Siminoff et al. 2006; Bao et al. 2007). Nevertheless, in this review the socioeconomic status of CRC patients could not be considered a predictor of adherence on its own.

The healthcare-system barriers that led to non-adherence were identified in two studies (Schneider et al. 2014; Chen et al. 2020), although these barriers had a minimal bearing on the patients' adherence behaviour. This included receiving late medication deliveries and receiving unclear instructions when starting the treatment. Other

studies have identified shorter duration of prescription refills (Accordino and Hershman 2013), ineffective patient-clinician communication (Ruddy et al. 2009), conflicting information regarding consequences (Eliasson et al. 2011), and patient satisfaction with information received (Efficace et al. 2012; Jacobs et al. 2017) as significant correlates of poor adherence to oral chemotherapy therapies. In a study exploring chronic myeloid leukaemia (CML) patients' reasons for not adhering to imatinib, Eliasson et al. (2011) suggested that there may be some mismatch in communication between healthcare clinicians and CML patients'. The interview data suggested that very few patients would bring up nonadherence issues with the clinicians involved in their care, and it seemed that patients believed nonadherence had little impact on their clinical response. While CML patients appear to rely on the clinician to let them know if their response is being negatively affected by their nonadherence, clinicians often focus on providing patients with positive feedback without being aware of the issue. Muluneh et al.'s (2018) research also discovered there was a major difference between what the patients were reporting and the guidance provided to patients on how to take oral chemotherapy medicines. It was also reported that patients' inability to read and understand the prescription label, which included the timing of dose intake with food, increased their risk of forgetfulness.

The Jacobs et al. (2017) study found improved satisfaction with clinician communication and treatment as the most robust predictor of better adherence. Patients who reported improvements in their perceptions of being understood and respected by their oncologist, being involved in health-related decisions, being able to

communicate with staff when needed, and having trust and confidence in their oncologist were more likely to adhere to their treatment. Furthermore, according to two studies (Simons et al. 2011; Sugita et al. 2016), patients may develop a good understanding of how to take oral chemotherapy medication with regular medication counselling. A review of the literature on the efficiency of various teaching strategies in cancer therapy recommends that teaching methods should be individualised and based on the patient's preferences, rather than provided uniformly (Hartigan 2003). It may therefore be beneficial to encourage CRC clinicians to initiate open and non-judgemental discussions about adherence that involve patients in decision making, as this can increase treatment satisfaction and patient knowledge, which may lead to improved medication adherence.

2.6 Limitations

There are some limitations to this review that should be considered. Although a thorough search was conducted, there may have been bias in the studies that were selected from the literature search. For instance, where no specific results section relating to CRC patients was reported, the grey literature of studies examining multiple cancer diagnoses was excluded. Also, it is important to exercise caution when generalising the medication adherence rates for indirect methods because the data obtained from six studies make it difficult to evaluate the scales' reliability and validity, as well as the range of methods used to measure medication adherence.

Another potential limitation is that, despite the risk of bias appraisal tool's structure and ease of adaptation for the specific needs of this review, it was difficult to reach an agreement on some of the checklist domains. For example, the outcome measure domain was largely graded as unclear because it was difficult to establish the validity of the instruments used. Also, each of the domains can be interpreted in different ways, and how easy it is to reach a consensus depends in part on the type of study that is being assessed. For instance, some studies had clearly defined factors and outcome measures, while other studies used several measures to assess adherence, which required more preparatory work to arrive at a consensus. Finally, the study was unable to distinguish between colon and rectal diagnoses since many studies did not draw a distinction between the two diagnoses.

2.7 Conclusion

Adherence to oral chemotherapy treatment is influenced by a variety of factors, which is a new feature of cancer care in the last decade. With advancements in cancer research and treatment guidelines for colorectal cancer, the patient's role in medication management has become critical for optimal care. Patient choice has made it important to adopt a treatment plan, which should be taken into account in all facets of the treatment plan.

There were variations in the definitions of adherence, and because each study was subjective, there was no consistent criterion for when a patient was considered adherent to their medication across the studies. In addition, the methods used to assess adherence varied between studies. Direct methods are an expensive tool that

can increase the workload of healthcare personnel and can be influenced by the patient. In addition, as the number of oral chemotherapy agents in development continues to grow, accurate measures of serum or urine metabolites are not always available for all medicines and therefore are not easily measurable in a clinical setting. Indirect methods, on the other hand, are relatively inexpensive and easy to implement. However, there is a risk of overestimating patient adherence when using indirect methods, both through self-reporting and by healthcare professionals. This is because patients may not always accurately report their medication use, and healthcare professionals may not be able to accurately assess patient adherence based on indirect measures alone, such as prescription refill data or pill counts.

Forgetfulness and the side effects of oral chemotherapy medications were the leading causes of non-adherence. However, many studies used quantitative approaches to identify non-adherence factors, and the reasons, such as the patients' influence on adherence and the socioeconomic implications of self-medicating at home, are still not understood. This could be because the influencing factors are often complex, with multiple interconnected causes. As a result, the quest for factors that influence adherence must be supplemented by the search for understanding, which involves a more interpretive and comprehensive approach.

There has been little qualitative research that explores the underlying causes and identifies the factors influencing adherence in colorectal cancer patients to oral chemotherapy medication. Patient-tailored treatments may be informed by a greater understanding of adherence in colorectal cancer patients receiving oral

chemotherapy. The way in which patients manage their symptoms and knowledge of their oral chemotherapy treatment must progress beyond the information received from their clinical teams. Qualitative research is a useful approach and triangulating the findings can help with understanding the challenges and sometimes complex reasons that influence medication adherence. It is equally important to consider the patient's beliefs about the prescribed medication with supporting adherence. This may assist clinicians to obtain a better understanding of how CRC patients' beliefs about oral chemotherapy treatment influence their medication-taking behaviour, which may lead to enhanced communication and open discussions regarding adherence decisions. This would also reduce the knowledge gap and give patients confidence in managing their medicines, especially when experiencing adverse effects or discontinuing their treatment.

2.8 Research Question

What Physical, Emotional, and Social Factors Influence Colorectal Cancer Patients' Adherence to Oral Chemotherapy Treatment at home in South Wales?

2.8.1 Aim and Objectives

The aim of this study was to explore the factors that influence colorectal cancer patients' adherence to oral chemotherapy medicines at home in South Wales. The objectives include to:

- Explore the challenges to oral chemotherapy medication adherence and identify factors that influence medication taking behaviour among colorectal cancer patients.
- Assess sociodemographic status and medication adherence using the Medication Adherence Report Scale (MARS).
- Examine patients' beliefs about treatment influence (necessity and concerns) and commonly held beliefs about medication using the Beliefs about Medicines questionnaire (BMQ).
- Triangulate the evidence sources to develop a comprehensive understanding of the phenomena and offer recommendations for research and clinical practice.

Chapter Three

Methodology and Methods

3.1 Introduction

This chapter will consider the philosophical grounding of the research that underpinned the qualitative case study research methodology and methods. This chapter will then outline the case study research approach and theoretical propositions that underpin this study. An exploratory embedded single case study with two analytical units was used in this research. This chapter then considers the sampling strategy, which includes information about the research setting, recruitment, sampling, and the inclusion and exclusion criteria. The materials and tools for data collection are then described, as well as the rationale, how the methods support the research aims and objectives, and the challenges with data collection. Details will be provided on how the data was analysed. This will include the analysis for the questionnaire surveys and the thematic analysis process that used a framework method of analysis. This chapter next evaluates the research's quality and discusses the data management and confidentiality issues that were considered. Lastly, the ethical considerations and research committee approvals are outlined.

3.2 Research Paradigm

Guba and Lincoln (1994) suggest that the research paradigm should be explored prior to the consideration of research methods. This is because the paradigm in which the

researcher positions themselves defines how they view the world (Crotty 1998), which consequently makes up the foundations of the research and shapes the nature of the study. The authors suggest that the design of the research is dependent upon three fundamental principles that define what falls within and outside the limits of legitimate review. These principles combine beliefs about the ontological question, which is concerned with beliefs about what there is to know about the world (Crotty 1998). At one end of the spectrum is the belief that reality is objective and that there are universal truths about reality that can be known. At the other end is a belief that reality is subjective and contextual, and a universal understanding of psychological experiences cannot be obtained because they must always be understood within the contexts within which they are embedded (Hays and Singh 2012). Epistemology is *“the nature of the relationship between the knower or would-be knower and what can be known ”* (Guba & Lincoln 1994, pg.201). In other words, in research, epistemology is used to describe how we come to know something and what counts as knowledge in the world. It is concerned with the very bases of knowledge – its nature, how it can be acquired and communicated to other individuals. The final principle being the methodological question about how the researcher (would be knower) goes about finding whatever can be known.

The researcher is positioned within a constructivist paradigm, believing that people’s experiences and their understanding of the world around them are shaped and constructed through social activity, and interaction, and are influenced by many factors (Thomas et al. 2014). The constructivist worldview assumes that knowledge is constructed rather than discovered. It is constructed individually through the

meanings and understandings developed socially and experientially (Guba & Lincoln 1994). Within a constructivist paradigm, the individual is at the centre of the meaning making experience (Thomas et al. 2014). The researcher utilised a constructivist approach to explore the perspectives of different CRC participants on the factors influencing oral chemotherapy medication adherence, focusing on how their various meanings shed light on this research. As a result, the diversity of perspectives enriches our understanding of the various ways in which reality has been experienced.

The interaction between the researcher and the participant, while allowing participants to express their experiences, is one benefit of the constructivism approach (Crabtree and Miller 1999). Thus, as a constructivist researcher, it is important to engage with the participants throughout the process of data collection (e.g., from study recruitment through to interviews) to ensure that their social reality is mirrored by the knowledge that is produced. As constructivists believe that individuals develop subjective meanings of their social experiences that can be quite diverse in nature, the researchers' role is not to constrict the meaning of a situation into a small number of categories, but rather to broaden this meaning and explore the complexity of these different views (Creswell and Creswell 2018). By adopting a constructivist approach, participants are able to convey their perceptions of reality through their stories, which helps the researcher better understand the participants' behaviour (Baxter and Jack 2008). In relation to this study, the researcher was therefore sensitive and mindful of the multiple and unique perspectives and experiences that were shared throughout this study and vigilant about how they were interpreted and consequently reported.

Case study research, as a methodology, has a practical flexibility in its approach in that it does not precisely fit into a fixed ontological and epistemological paradigm (Rosenberg and Yates 2007; Harrison et al. 2017). As Luck et al. (2006) argues, case study research has the potential to bridge the gap between the traditional research paradigms in the context of health and social sciences research. Harrison et al. (2017) suggest that authors such as Stake (1995) have an approach to case study research that is closely aligned with a constructivist and interpretivist orientation. On the other hand, Yin (2017) describes how his approach is oriented towards a 'realist perspective' (pg. 16). Baxter and Jack (2008) consider the approaches of both Stake and Yin to be guided by the constructivist paradigm. However, both Yin and Stake do not make their epistemological positions clear (Takahashi and Araujo 2019) although Yin suggests that the case study method can embrace different epistemological orientations (Yin 2017, pg. 16).

In relation to this study, Yin's (2017) methods informed the design of the research (i.e., an embedded single case study). Although it is acknowledged that this approach may not offer comprehensive guidance on pursuing a relativist or constructivist approach (Boblin et al. 2013), it does offer relevant and structural guidance for doing such case studies (Yin 2017). To help shape the case study, Yin suggests, for instance, constructing some preliminary theoretical propositions (see *Table 3.1*) that represent practical matters or key issues that have arisen from the literature. For example, drawing on the WHO framework's wider set of determinants that influence adherence to oral chemotherapy agents.

3.3 Exploration of Methodology

This research provides an exploration into CRC patients' perspectives on the factors that influence adherence to oral chemotherapy medicines in South Wales. It explores their beliefs about their medicines and seeks to identify factors that influence medication taking behaviour. To explore patient adherence issues, it was necessary to gain an understanding of the participants' experiences as they construct them in their own context.

Quantitative research tends to be more connected to the positivist paradigm. A known, predefined method is used to measure the numerical values that form the basis of quantitative designs. The data is often collected from a large sample size, and statistical analysis can be used to interpret numerical data. It is also largely objective in nature, with a goal of generalising findings to a group that extends beyond the participants (Polit and Beck 2008). Qualitative research, however, refuses to limit its questions and methods beforehand. The qualitative methods focus primarily on the participants' reported experiences, which are explored through interaction with the researcher. Typically, the data obtained offers a rich, in-depth, descriptive account of events, allowing the researcher to acquire specific findings. The accounts are analysed, themes are derived from the study, and findings can be drawn from the analysis. When the theory in the area is not well defined, qualitative approaches are frequently employed from which further research can then be conducted (Silverman 2013). This study employed qualitative case study research in order to provide a transferable, in-depth analysis of the complexity of adherence decision-making

among CRC patients receiving oral chemotherapy treatment. The exploratory research is not intended to provide definitive evidence but rather to increase understanding of the phenomenon. A follow-up study, building on the research findings, can be used to inform education tools and policies that meet the needs of the patient population and improve healthcare service and practice.

A case study method involves a detailed, close analytical investigation of a single subject, such as a location, group, organisation, event, or instance (Yin 2017). The key feature that distinguishes this as a case study is that the researcher is conducting research with only one group of individuals, which is CRC patients' residing in South East Wales, as opposed to gathering data from individuals in various settings.

3.4 Case Study Research

Qualitative case study research is increasingly used in numerous social science disciplines and professional settings, such as nursing, political science, and health psychology (Anthony and Jack 2009). It is also prominent in other disciplines such as education (Gulsecen and Kubat 2006) and community-based problems when socioeconomic issues (e.g., poverty, unemployment) are raised (Johnson, 2006). This research method involves the study of a 'case' (or cases) that is in a current, real-life setting to gather accurate information over time (Yin 2014). It is a qualitative approach that involves collecting in-depth, detailed data using multiple sources of information and producing descriptive reports and themes of the case (Creswell and Creswell 2018). Yin (2017) explains that case studies let you focus in great detail on a 'case' and

allow you to retain a holistic and real-world outlook, for example, by studying small group behaviour, organisational and managerial processes, international relations, and individual life cycles.

Yin (2017) defines case study as a two-part research method, the first of which is the scope of a case study. The first segment investigates a contemporary phenomenon ('the case') in detail to understand a real-world case and be able to distinguish case studies from other modes of context (Yin 2017). The second segment of the definition develops when the phenomenon and other modes of context are not distinguishable in real-world cases. In these situations, other features of a case study are significant. A case study has a comprehensive mode of analysis underpinning the design, data collection, and particular approaches to data analysis. Additionally, case studies focus on the triangulation of data using several sources of evidence (Yin 2017). In general, case study research comprises an all-encompassing mode of inquiry, with its own logic of design, data collection techniques, and specific approaches to data analysis.

Yin (2017) outlines three conditions that should be met if a researcher intends to conduct case study research. These criteria include the type of study question addressed, the amount of control a researcher has over actual behavioural occurrences, and whether the phenomenon under consideration is contemporary or historical. The research question is normally categorised as 'who, what, why, where and how' questions (pg.10). There are certain 'what' questions that are exploratory in nature, such as 'what are the implications of the COVID-19 pandemic on healthcare cancer services? This type of question can be a suitable justification for doing an

exploratory case study. For example, given the COVID-19 pandemic is a relatively new phenomenon, the study can generate initial knowledge about the phenomenon's implications for cancer resources (i.e., availability of intensive care beds, waiting times for diagnosis and treatment). The second category of 'what' questions are those that follow the "to what extent" path of inquiry. For instance, a question such as "To what extent have CRC patients in South Wales assimilated to the new oral chemotherapy treatment?" is more likely to be investigated using survey methods or archival data when the objective of the research is to track specific outcomes or describe the incidence or prevalence of a phenomenon, and a case study will not be very useful in this instance.

Additionally, case studies further mandate that the researcher should not have control over the actual or behavioural events in the study. Thus, it was necessary that the researcher have no personal control over the actual or behavioural events. Lastly, the phenomenon being studied is also current, and not historical. As a result, the researcher is confident that this study meets the three requirements outlined by Yin (2017) for case studies.

Case studies have been categorised in a variety of ways; Hakim (1992) divides them into three groups: descriptive, experimental, and selective. Burns (2000) classifies case studies into six categories: historical case studies, oral history, situational analysis, multi-case studies, observation, and clinical case studies. Yin (2017), on the other hand, classifies three types of case studies: explanatory, exploratory, and descriptive. Explanatory case studies are defined as explaining causal links in real life situations;

exploratory case studies are defined as exploring a real life situation with no single outcome; and descriptive case studies are defined as describing a phenomenon in a real life context. This emphasises the fact that case studies can be classified in a variety of ways.

While case study research's key strength is its ability to explore complex issues in a current, real-life setting in order to acquire in-depth information, the limitations of the methodology must also be acknowledged. Due to the lack of rigour in single case studies, the generisability of the findings has been questioned compared to other types of qualitative research (Merriam 2009; Yin 2017). Shields (2007, pg. 13) argues that the strength of qualitative approaches is that *"they account for and include differences ideologically, epistemologically, methodologically, and, most importantly, humanly"*. Case studies can provide opportunities for the researcher to immerse themselves in complex settings and without attempting to eliminate what cannot be discounted.

Therefore, for this study, the plan was to provide a transferable, in-depth analysis of the complexity of adherence decision-making among colorectal cancer patients receiving oral chemotherapy treatment. The criteria for assessing the quality of this research can be found in *section 3.5.5*. Furthermore, although a rich, thick description is desired, the researcher can encounter difficulties with the large amount of data that is produced and with the selection of what details to use, what data to collect, and the analysis process to use (Merriam, 2009). It is therefore important for the researcher

to justify and make explicit the decisions made throughout the collection, analysis, and reporting of the data.

3.4.1 Case Study Research Design

Yin (2017) explains that there are five measures of a case study that are central to the research design. These are:

- **Research question:** The research question aims to explore the factors that influence adherence to oral chemotherapy medication and therefore will apply a “*what*” type question. Yin (2017) determines that this type of question is a justifiable rationale for conducting an exploratory study, and the form of the question provides an important indication with respect to the most relevant research method to be used (Yin, 2017). It is therefore important to clearly identify the nature of the research question.
- **The study propositions:** Yin (2017) argues that exploratory studies may not have a specific study proposition, but a clear purpose and the criteria should be outlined. The theoretical propositions (*see section 3.4.2*) take into account both the findings from the literature review and the factors that were identified in chapter 1 (*see section 1.6*), which were categorised in accordance with the WHO (2003) framework for adherence to long-term therapies. The theoretical propositions served as the basic foundation upon which the study’s direction was based.

- **The ‘case’:** The ‘case’ for this study was *adherence to oral chemotherapy medicines*. The case was selected to maximise the opportunities for developing hypotheses or theories that explain the social phenomenon at hand and are based on empirical considerations (Bleijenbergh, 2012). The boundaries of the case are colorectal cancer patients living in the South East Wales region. Bounding the case tightens the connection between the case and the research question; therefore, it is important to make the distinction clear.
- **The logic linking the data to the theoretical proposition:** According to Yin (2017), one of the researcher’s strategies is to collect case study data as a reflection of the theoretical proposition. Consequently, data collection and analysis methods were chosen to maximise the opportunity to detail a more complete picture of participant perspectives of the factors influencing oral chemotherapy medication adherence. The sources of data were questionnaire surveys and semi-structured interviews. Please see sections 3.5.3 and 3.5.4 for more information on data collection and analysis methods.
- **The criteria for interpreting the findings:** An important strategy for case study research is to identify and address opposing explanations of your findings. Yin describes that addressing the work of rivals is a criterion for interpreting the strength of your findings (Yin, 2017). As a result, when interpreting the results, the researcher was mindful of competing explanations for the data collected, as well as the fact that the participant responses could be influenced by a variety of factors, such as the researcher’s relationship with the participants, the researcher’s role, and conflicts of interest. Consequently, ethical considerations of

the research and data that were analysed, as outlined in section 3.7, were important.

3.4.2 Theoretical Proposition

The theoretical proposition represents the key topics from the research literature and the theoretical framework. The conceptual issues of adherence mentioned in chapter one, the literature review, and the WHO framework provided the researcher with a clear concept from which to develop ideas for deciding what data to collect, for example, creating the interview topic guide and the approach for analysing the data. The WHO framework classifies the main factors that influence adherence to medicines into five key groups (see *section 1.6*). Yin (2017) suggests that the initial theory statements be clear-cut and provided alongside a rival theory that might help mould the case study. Yin (2017) argues that theory statements should by no means be considered with the formality of grand theory but rather, provide a sufficient blueprint for the study. Sutton and Shaw (1995 pg. 378) describe the theoretical proposition as a *“hypothetical story about why acts, events, structures, and thoughts occur”*, resulting in a comprehensive research design, ideas for selecting the data to collect, and approaches for data analysis.

Table 3.1 Theoretical propositions

Theoretical Proposition	Rival Proposition
Participants belief that adherence to the oral chemotherapy medicine is necessary.	Participants belief that there is no benefit to be gained from adherence to the oral chemotherapy medication.
Treatment toxicity and side effects is a key reason for poor adherence and makes it difficult to adhere to a dosing regimen.	Treatment side effects has no influence on participants adherence decisions.
Participants from lower sociodemographic areas in South Wales may have lower adherence rates owing to socioeconomic challenges like lack of support systems and financial difficulties.	There is no association between medication adherence and different sociodemographic groups in South Wales. However, lack of understanding about their treatment could have an impact on their adherence.
Participants are highly adherent to their medicine owing to the severity of the disease. There may however be some unacknowledged anxiety and depression in this cohort.	The severity of the disease is not a key determinant of medication adherence. Participants cope well with psychological difficulties associated with the treatment and CRC diagnosis.
A positive relationship between participants and CRC healthcare clinicians involved in their treatment can help promote better adherence.	Although a good relationship with the doctor in charge makes participants feel important and optimistic about their treatment, communication with the CRC healthcare practitioners is not a factor.

3.4.3 Embedded Single Case Study Design

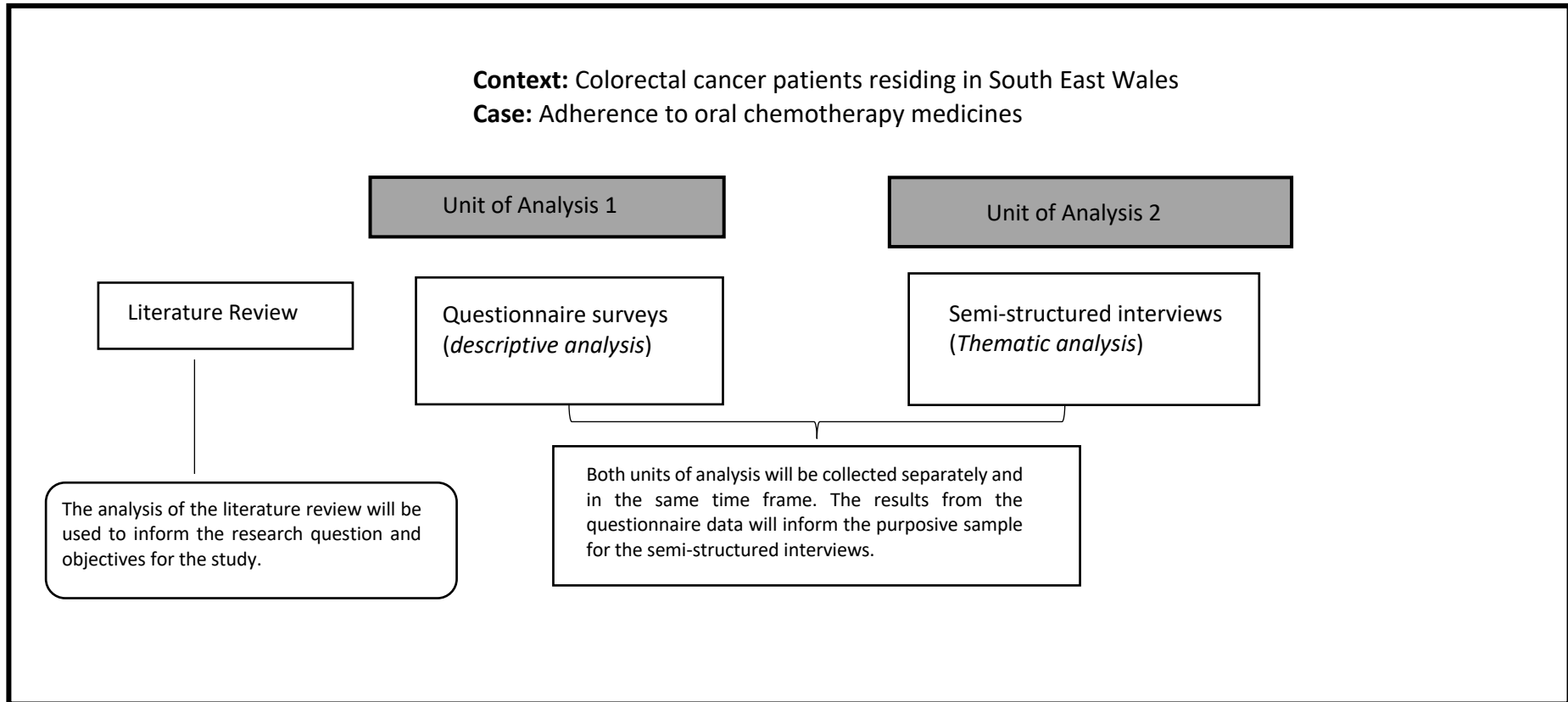
Case studies can be conducted using either single or multiple cases. The differences are when a study includes more than one single case, the researcher is looking to understand the differences and similarities between the cases (Baxter and Jack, 2008). According to Siggelkow (2007), the existence of a phenomenon can be richly described by single case studies. A single case study allows the researcher to question old theoretical relationships and investigate new ones, resulting in a more thorough study. This allows the researcher to gain a deeper understanding of adherence influencing factors to oral chemotherapy medicines. Yin (2003) further explains that

when the researcher chooses a single case study with embedded units, he gets the ability to explore those subunits that are located within the case.

For the purposes of the study, this research uses an embedded single case study design (*see below figure 3.1*). An embedded single case design allows the researcher to collect a deeper array of evidence that contains more than one unit of analysis in comparison to a holistic single unit design (Yin, 2017). The important distinction is that the embedded units are all part of the original single case study.

Yin (2017) argues that the single-case design imposes the boundaries, with the methods sharing the same research question, collecting complementary data, and conducting counterpart analysis (Yin, 2017). The design format allows the researcher to address broader, more complex questions, such as factors influencing adherence to oral chemotherapy treatment. The theoretical proposition sets out a clear set of conditions within which the framework is understood to be an accurate reflection. Yin (2017) states that the single case design can represent a significant contribution to the present theory by either endorsing its findings, challenging the theory, or adding to the knowledge base.

Figure 3.1 – flow diagram to illustrate the single case study design with Embedded Units of Analysis.



3.4.4 Data Collection

Qualitative research over the years has an evolving meaning and expresses an ever-changing nature of qualitative inquiry. According to Richie and Lewis (2003), these features include: the research's overall perspective, the study design's flexibility, the richness of qualitative data; specific approaches to data analysis and interpretation; and the types of outputs qualitative research generates. In order to obtain this knowledge, the research methods must be designed with the understanding of creating an environment in which participants can freely express themselves. Qualitative researchers therefore study things in their natural settings, trying to understand or interpret facts in terms of the meaning people bring to them. Angen (2000) explains how interpretive approaches rely heavily on naturalistic approaches such as interviews, observations, and analysis of existing documentary evidence. Yin (2017) contends that case study evidence can be derived from a variety of different sources, and he discusses six of them: documentation, archival records, interviews, direct observations, participant observation, and physical artifacts. These sources of evidence would ensure sufficient interaction transpires with the participants to gain a meaningful understanding of their reality.

It is important to note that qualitative researchers differ in how much they rely on specific data collection methods. This is because some qualitative researchers have argued that numerical data are incompatible with a constructivist research view, as these data indicate the existence of a single objective reality, measured and analysed statistically for generalisable outcomes (Maxwell 2010). However, Richie and Lewis (2003, pg. 38) argue that the use of qualitative and statistical investigations may be beneficial, provided that both

approaches and the data they produce can be clearly defined. Furthermore, although Denzin and Lincoln (2000, pg. 8) describe qualitative research as a collection of interpretive, material practises that makes the world visible, they do not, however, rule out the use of alternative methods, such as surveys, supported by paradigms other than those that are considered to be more naturally aligned. Indeed, Romm and Litt et al. (2013, pg. 657), alluding to a qualitative constructivist approach, argue that questionnaires can be used in a qualitative-constructivist context. These researchers suggest that this is an additional (and less common) approach to handling questionnaires and that both “mono- and mixed methods” studies can benefit from this method. The authors advise that when writing up and generating discussions about the research findings, the researcher should be reflexive and consider the potential impact of the questionnaire’s design and implementation.

The decision to use case study research stems from the desire to understand complex social phenomena, the case, rather than the underlying paradigm or methodology used (Flyvbjerg 2011). This study was more concerned with the appropriateness of the research methods used and the research question than with the philosophically coherent stance of conventional research methods. Streb (2012) explains that an exploratory case study supports providing insight into the structure of a phenomenon that is characterised by a lack of detailed primary research. This includes a lack of formulated hypotheses that can be tested and/or by a specific research environment that limits the choice of methodology. In addition, Bleijenbergh (2012) argues that researchers who use exploratory case studies choose a case that makes the best use of the opportunities to produce hypotheses or theories that explain the social phenomenon. The broad concept provides the researcher with a high degree of flexibility and independence with regard to the research design as well as the data collection, as long as

these fulfil the required scientific criteria of validity and reliability (Streb, 2012). An exploratory study, as a result, is not limited in terms of its qualitative or quantitative specificity. By including both quantitative and qualitative data, a case study helps explain both the process and outcomes of a phenomenon through the complete reconstruction and analysis of the cases under investigation (Tellis, 1997). Through the exploratory case study method, the researcher was able to go beyond the quantitative statistical results and understand the behavioural adherence decisions from the participant's perspective. Furthermore, measures such as credibility and transferability serve as a clear indication of the soundness of the research and its degree of flexibility, for example, in terms of data collection and the in-depth analysis of the social phenomenon.

The researcher recognises that qualitative and quantitative methods are not perfectly calibrated but sees this as a demonstration of the various ways that each method contributes to a better understanding of the phenomenon under study. Qualitative research fosters a dialogue between different ways of seeing, interpreting, and knowing rather than just merging different methods and types of data (Greene, 2007). The researcher was mindful of making assumptions when interpreting the data and making inferences about the greater generalisability of the findings. Nonetheless, the search was for complementary extension by using different forms of evidence to gain a deeper and more comprehensive understanding of the social phenomena than a single method could deliver.

For the purposes of the study, an embedded unit of analysis collected self-reported participant data to assess adherence rates to oral chemotherapy medicines, the participants' sociodemographic characteristics, and commonly held beliefs about their medication. The second embedded unit analysis consisted of semi-structured interviews to explore the potential barriers or challenges with adherence to oral chemotherapy medicines among CRC participants and the influences on medication-taking behaviour.

3.5 Methods

3.5.1 Research Setting

Wales consists of seven local health boards (LHBs) and three NHS trusts, which came into effect in October 2009 (NHS Wales, 2021). It is responsible for delivering all NHS healthcare services within a geographical area, replacing the previous system of twenty-two LHBs and seven NHS trusts, which together performed these functions in the past. The three NHS Trusts in Wales are the Welsh Ambulance Services Trust for emergency services, Velindre University NHS Trust, and Public Health Wales. Velindre University NHS Trust is responsible for Velindre Cancer Centre, which serves over 1.5 million people across South East Wales (NHS Wales, 2021).

Colorectal clinics are held in the mornings on Mondays, Wednesdays, and Fridays, with two clinics running concurrently. Medical oncology consultants oversee all clinics and are part of a multidisciplinary specialist care team. Patients that arrive at the clinic for an appointment must first check in at the reception desk. After checking in, patients are seated in the waiting

area, and the phlebotomist examines them if blood tests are required. The weight of the patient may also be recorded, which is usually conducted by the nurse. Those who do not require blood tests are seated in the main waiting area, where they will be examined by a clinician, who will also prescribe their next treatment dose.

3.5.2 Sampling Selection Strategy

3.5.2.1 Recruitment

The multidisciplinary colorectal care teams, which include doctors, nurses, and pharmacists, identified potential participants and made the initial approach to briefly explain the nature of the study. Permission to attend clinics and recruit participants was obtained via email from medical oncology consultants after the researcher received NHS research ethics committee approval and a letter of access from Velindre Research and Development (see *section 3.8*). It was important for clinicians to take part because they were directly involved in the care of patients receiving oral chemotherapy medication. They were essential in helping the researcher gain a better insight of the various challenges to medication adherence that individuals encountered. The presence of the researcher at their clinic was approved by four of the six consultants. Two consultants requested an interactive meeting to discuss the researcher's recruitment process and its influence on the clinic's operations. The researcher is a healthcare professional with experience working in clinical settings. I was aware that clinicians were unsure about their role in the study and the researcher's role in the clinics, so care was taken to clarify how this would operate while avoiding interfering with consultations. The researcher addressed each member of the clinical care team to explain the

purpose of the study, recruitment, and their role in the initial approach to participants. In addition, information sheets and consent forms for healthcare professionals were provided to read and sign before taking part in the study.

Care was taken to ensure that patients who were deemed too unwell by their clinicians or who were receiving palliative care were not recruited into the study. The outpatient clinic at Velindre University NHS Trust has a supportive care team with values of commitment to a patient-centred and compassionate approach in dealing with cancer patients. Participants were invited to take part in the study if they expressed interest after being identified by the colorectal clinical care team. The initial approach took place at the end of each consultation, at which point the clinician informed the patient (subject to meeting the inclusion criterion) about the research. Each participant was given a unique six-digit identification number to keep track of those that had been approached. Once there was interest from the patient, the clinician introduced the researcher and, at this point, approached the identified patient to provide them with more detail about the research and an information leaflet that covered the essential elements of the research.

The researcher had taken the required amount of time to ensure the essential details were explained thoroughly to the participant and any relevant questions about the study were responded to. Potential participants were given the duration of their time at the clinic (approximately two to three hours) to decide whether or not to take part in the study. This was likely to increase the response rate, taking into consideration the infrequent nature of eligible patients visiting the outpatient clinic and the timeframe of the study. Individuals were advised that, if they agreed to participate, they could withdraw their consent at any time

during the study without the need for an explanation. The consent form also provided the participant the opportunity to take part in all of the research data methods (*see Appendix 5*). If the person was happy to take part in the study, informed consent was obtained in writing by the researcher. This took place in a designated consultation room, at which point the participant would be given the option to complete the survey with the researcher.

If the individual required more time to consider their options, the researcher provided them with the relevant documents, which included an information sheet, a consent form, and a questionnaire survey to take home and read before deciding whether or not to participate in the study. The researcher requested permission to contact the participant by asking them to complete a response slip providing their name and contact number. The researcher scheduled a suitable time and day to speak with the participant to confirm whether they were satisfied with the information provided and to answer any questions. Individuals who were happy to take part were asked to bring the completed forms with them to their next scheduled review meeting.

3.5.2.2 Sampling Strategy

Qualitative research uses non-probability samples, which were used for selecting the population for this study (Ritchie and Lewis, 2003). In a case study, the 'case' (adherence to oral chemotherapy medicines) is of utmost importance, and the research sought to produce a sample rich in information (Patton, 2002). The sample was not intended to be statistically representative, but instead the characteristics of the population were used as the basis for selection.

Unit of Analysis 1 (Questionnaires)

The questionnaires sought to produce a sample to provide insight into medication adherence and beliefs about the oral chemotherapy medication among CRC participants in South Wales. Prior to any clinical eligibility checks, approximately 2 to 4 patients per clinic were receiving oral chemotherapy medication. For a period of four months, the same group of patients would return for cyclic appointments every three weeks. A predetermined quota of approximately 36 to 90 patients were approachable to take part in the first unit of analysis over the eight-month period of data collection. Patients who were further along in their treatment at the time data was collected, patients who were clinically ineligible, potential dropouts, and condition exacerbation were all taken into account. The most suitable selection process within the time frame was convenience sampling, and all patients that met the inclusion criteria were approached to take part in the study (Patton, 2002). This form of sampling was deemed appropriate for this study given the accessibility of eligible colorectal cancer patients that could potentially be recruited into the study.

Unit of Analysis 2 (Interviews)

The results from the first units of analysis informed the selection of the sample population, and only participants who could enrich the study with knowledge of the phenomenon were invited. Case studies require an information rich sample, therefore a purposive sample was used (Patton, 2002) of participants with a range of high (MARS=40) and lower (MARS<40) MARS scores of reported adherence from the first unit of analysis. This was done to ensure that participants with different adherence scores had their perspectives on the case explored. In addition, this method is appropriate when there is a need for participants to possess

research-critical traits so that they can offer the required information (Patton, 2002). Participants were selected to explore the challenges with medication-taking behaviour and emerging issues with factors influencing adherence to oral chemotherapy treatment. In general, qualitative case study researchers adopt the principles and notions of data saturation in terms of no new data, no new themes, no new coding, and the ability to duplicate the study (Aguboshim 2021). This approach was used by the researcher, and interview data collection continued until no new topics surfaced and the saturation point was achieved, as determined by peer debriefing with the supervisory team. Various procedures, such as peer debriefing with two experts in qualitative research and triangulating the different sources of evidence, mitigate any concerns about the research's credibility.

3.5.2.3 Inclusion Criteria

- Patients who are being treated for colorectal cancer and have been prescribed an oral chemotherapy medication at Velindre University NHS Trust.
- Patients must have taken their treatment for at least the first treatment cycle in order to stabilise on their medication and reduce the risk of discontinuation during this phase.
- Patients from the South East Wales region.
- Participants over the age of 18 and who were able to read and respond in English.
- Willing to participate in the study and able to provide informed consent.
- For Interviews: participants who agreed (with written consent) to take part in an interview and agreed to have an audio device record the events.

3.5.2.4 Exclusion Criteria

- Not receiving treatment for colorectal cancer and not prescribed oral chemotherapy medication.
- Patients starting their first cycle of oral chemotherapy medication.
- Patients with clear intellectual impairment were excluded from the study. Prior screening was carried out with the participant by briefly discussing with them the nature of the research and confirming they understood.
- Patients deemed by the clinical staff to be too ill to take part or who were receiving palliative treatment.
- Not provided informed consent to the interview and are not willing for an audio device to be used.
- Do not live in South East Wales.
- Is unwilling to participate in the study and provides no informed consent.
- Is under the age of 18 and cannot read or respond in English.

3.5.3 Materials and tools for Data Collection

3.5.3.1 Questionnaire Surveys

Questionnaire surveys provide the case study researcher with a data-gathering technique that collects, through self-reports, either quantitative or qualitative information from an individual regarding their knowledge, beliefs, opinions, or attitudes about or towards a phenomenon under investigation (Mills et al. 2012). It is important to note that the quantitative data from the questionnaires was not used to determine causal relations but to

complement inferences drawn from the qualitative analysis. As a social constructivist, the researcher was searching for what is unique to the individual about their adherence decisions, how they create their social realities, and how they interpret the factors that influence their adherence to oral chemotherapy medications.

A three-part self-report questionnaire survey was distributed to participants. The first segment addressed health-related questions to capture important details in regard to the participants' socio-demographic status. The second segment assessed participant adherence to oral chemotherapy medication, and finally, the third segment examined participant beliefs about the oral chemotherapy medicine. Further information about each segment can be found in this section.

3.5.3.1.1 Sociodemographic Characteristics

The South Wales region accounts for around 30% of the Welsh population, with the cancer incidence rates varying greatly, particularly in less affluent areas (WCISU, 2015). It was important for the researcher to obtain sociodemographic data from patients to explore whether disparities in medication adherence existed between affluent and less affluent locations (more detail is provided in *section 3.5.4.1.1*). Data was collected in reference to their age, gender, marital status, educational level, and area or location of residence. The participants' cancer status, current treatment(s) for their condition, the number of prescribed oral medications, and the name of the oral chemotherapy medication currently prescribed were also included in the data. Along with the initial checks completed by healthcare

practitioners, the researcher was able to use demographic and treatment characteristics to determine if participants satisfied the inclusion criteria.

3.5.3.1.2 Medication Adherence Report Scale (MARS)

The Medication Adherence Report Scale (Horne and Weinman 1999; Horne and Weinman 2002) is a 10-item self-report scale that assesses both intentional and nonintentional adherence. In order to reduce social desirability bias and normalise the concern of non-adherence, MARS statements such as 'I stop taking it for a while', are phrased as negative statements (Chan et al. 2019). The questionnaire items have been shown to be reliable in predicting non-adherence across long-term conditions such as asthma, inhaled corticosteroid (ICS) use, and hypertension (Horne and Weinman 2002; Cohen et al. 2009; Chan et al. 2019). Cohen et al. (2009) assessed the psychometric properties of the MARS for asthma tool (see *Table 3.2*) among low income, English and Spanish speaking patients' with asthma. Internal validity was assessed using Cronbach's alpha and test-retest correlations, which showed good inter-item correlation in English and Spanish (Cronbach's alpha = 0.85 and 0.86, respectively) and good test-retest reliability ($r = 0.65$, $P < 0.001$). Construct validity (correlating self-reported adherence with medication beliefs) was also good, with self-reported adherence higher in those saying daily ICS use was important and ICS were controller medications ($P = 0.04$). While many studies, including cancer groups, have used a shorter 5-item form of MARS (see *section 1.5.4*), there has been variability in its reported accuracy in conditions such as chronic obstructive pulmonary disorder and diabetic patients receiving oral hypoglycaemic agents (Tommelein et al. 2014; Vluggen et al. 2020).

Table 3.2 The Medication Adherence Report Scale for Asthma (Cohen et al. 2009)

Items	
1	I only use my (*name of medicine*) when I need it
2	I only use it when I feel breathless
3	I decide to miss out a dose
4	I try to avoid using it
5	I forget to take it
6	I alter the dose
7	I stop taking it for a while
8	I use it as a reserve, if my other treatment doesn't work
9	I use it before doing something which might make me breathless
10	I take it less than instructed

The MARS questionnaire for asthma consists of 10 items as shown in *Table 3.2* and evaluates the frequency of non-adherent behaviour, assessed on a 5-point Likert-type scale with the options: 'never (5), rarely (4), sometimes (3), often (2) and very often (1). Self-reported adherence is reported as the average of the 10 questions, with higher scores indicating higher levels of reported adherence to medication. In relation to this study, two asthma-specific items were removed from the original 10-item scale (Item 2: *"I only use it when I feel breathless"* and Item 9: *"I use it before doing something which might make me breathless"*). These items were removed because they were not relevant to the CRC research cohort receiving oral chemotherapy agents. The researcher acknowledges that caution should be exercised when interpreting results using unvalidated tools for specific target populations, and *section 6.10* considers the implications of removing items from validated tools.

3.5.3.1.3 Beliefs about Medicines Questionnaire (BMQ)

Patient's beliefs about prescribed medicines are thought to influence medication adherence (WHO 2003; Lin et al. 2017). The Beliefs about Medicines Questionnaire (BMQ) was

developed by Horne et al. (1999) as a measure of patients' beliefs about medication adherence and has been validated for use in chronic illness groups (Komninis et al. 2013; Jimenez et al. 2017). In studies on adherence to oral anticancer agents, perceptions of illness and beliefs about their medication have become more prominent in breast cancer (Tan et al. 2022), chronic multiple leukaemia (Lea et al. 2018), haematology settings (Verbrugghe, Timmers, Boons, Van, et al. 2016), and patient groups with diverse cancers that include CRC (Bhattacharya et al. 2012; Timmers et al. 2016).

There are two categories of beliefs that influence how participants feel about taking prescribed medications: necessity (the feeling of a personal need for treatment) and concerns (of the potential adverse effects of medications). According to Horne et al. (1999), when faced with competing demands, patients who believe their medication is unnecessary may purposely ignore it, lower their doses, or forget to take it. Likewise, patients who are concerned about taking the oral chemotherapy medicine may restrict their exposure to the agent to lower their risk (Bhattacharya et al., 2012). Understanding patients' knowledge, beliefs, and concerns about medication has an impact on how and whether people take their prescribed treatment, according to evidence based recommendations for healthcare providers (NICE 2009). Patients may have pre-existing views about their condition or treatment, which can have a great influence on how they view the treatment, the side effects, and the benefits of adherence.

3.5.3.1.4 Think Aloud Approach

One of the most notable learning points from the questionnaire pilot was that elderly patients (those over 65 years old) had great difficulty reading and interpreting the questions on their own, which made it difficult for them to respond competently. The data gathered from self-report tools is only as useful as the individual answering the questions and how they have interpreted the information. Mills et al. (2012) state that questionnaires are a subset of general survey techniques that include gathering information through oral responses as a means of data collection. As a result, questionnaire data was collected from participants at the clinic using the think aloud method. The think aloud approach is a research technique in which participants express their thoughts aloud while performing their task (Ericsson and Simon 1993).

Concurrent and verbal reports are widely regarded as important sources of information about a subject's cognitive processes during specific tasks (Anderson, 1987). Ericsson & Simon (1993) state that the closest connection between thinking and verbal reports is found when subjects verbalise thoughts generated during task completion. When people are asked to think aloud, some of their words appear to be simply vocalising what would otherwise be inaudible inner speech. Ericsson and Simon (1993) defined three levels at which an individual can verbalise their thoughts and processes: simple vocalisation, verbalization that incorporates a description or clarification of the thought content, and verbalization that involves the subject in explaining his thought processes. This research aligned with the first level of simple vocalisation, in which participants were not required to exert any effort in order to explain their responses. This category was chosen because the participants were able

to interpret the instructions and respond to the statements that were read aloud. The participants were prevented from deviating from the task at hand by using this method, as they would otherwise have needed to draw on additional thoughts and explanations.

The researcher's approach was to first explain to the participant how the questionnaire would be conducted. In addition, to minimise the social aspect of the procedure, participants were informed that no explanations would be required for their responses. To ensure they understood the task, the researcher carried out simple practice attempts by reading aloud statements, for example, "*please can you confirm your name?*" and "*are you currently taking oral chemotherapy tablets?*". Furthermore, before marking the chosen answer, the researcher reaffirmed the participant's response by repeating it back to them.

3.5.3.2 Semi-structured Interviews

One of the primary applications of case studies is the use of qualitative interviews to interpret participants' experiences and perceptions (Brinkmann, 2014). Also, semi-structured interviews are the most common type of interviews used in qualitative research and the healthcare context (DeJonckheere and Vaughn 2019). It was important that the information obtained from the interviews was relevant to the research aims. For this study, semi-structured interviews were chosen as an appropriate source of evidence because participants were able to share their experiences, attitudes, perceptions, and beliefs related to the challenges of adhering to oral chemotherapy medicines. Interviews can support the research with rich explanation (i.e., the how and why questions) to further explain key topics and

provide a pertinent perspective reflecting the participants' beliefs about taking oral chemotherapy medication.

Yin (2017) explains that the researcher will have two roles during an interview used as case study evidence. Firstly, the researcher should follow their own line of inquiry. Instead of following a structured line of inquiry, the interviews followed a topic guide that was informed by the literature and theoretical propositions and served as a holistic framework for the discussion (WHO, 2003; Horne and Weinman 1999; Horne et al. 2001; Horne and Weinman 2002c). This allowed the researcher to provide structure based on their interest in the subject area while also allowing the participant flexibility to voice their experiences and provide a descriptive narrative (Brinkmann, 2014). Please refer to *Appendix 7* for the interview guide and the broad themes that were related to the research question.

The researcher's second role is to articulate the questions in an informal, unbiased style that serves the needs of the line of inquiry (Yin, 2017). The researcher used open-ended questions and phrased them in a way that allowed the participants to freely express themselves and discuss their views from their own perspectives. In addition, the literature has shown that patients tend to underreport non-adherence to their medication (Garber et al. 2004; Osterberg and Blaschke 2005; Rifkin et al. 2010) thus the line of inquiry into the case (adherence to oral chemotherapy medicines) was prompted on multiple occasions and approached in several different ways. Regarding patient-related issues, for example, participants were asked whether they would forget to take a medication dose and what conditions would cause them to do so. The researcher would listen to the details in the response and then give examples of common situations in which patients can forget to take

their medication (e.g., attending a social event, disruptions to routines, morning, or evening dose, etc.) and ask if such situations would apply to them. As a result, the same line of inquiry is used, but the subject in question is approached in a different manner. Throughout all of the interviews, probing questions were used to try to elicit as much detail as possible, allowing participants to provide detailed responses.

3.5.3.2.1 Interview Procedure

All participants were given the option for the interview to be held face-to-face at the clinic, on the Eastgate House university campus, or via a telephone meeting. Due to the length of time participants had spent at the clinic and transportation constraints, the difficulties of conducting the interviews at the clinic or Eastgate House were acknowledged. A designated consultation room at the clinic was arranged for face-to-face meetings to take place. In addition, those participants who made their own travel arrangements to attend an interview would be reimbursed for travel expenses. All participants, however, opted for telephone interviews since they were more convenient.

Fifty-five participants who completed the questionnaire indicated that they would like to be contacted for a follow-up interview on the survey form, though three participants did not provide sufficient information to enable contact. The MARS data from the questionnaires were used to select a purposive sample of participants for interviews. Participants with a range of adherent (MARS = 40) and non-adherent (MARS < 40) MARS scores were chosen. Three participants could not be contacted to arrange an interview, and one person cancelled

after an interview had been scheduled. No new themes emerged after 16 interviews, and this formed the final sample for this study.

Each interview started with an introduction and an explanation of the research's purpose, aims, and objectives, as well as levels of confidentiality and discussion topics. An audio recorder was used to provide a more accurate account of the interviews, which were subsequently transcribed verbatim by the researcher. The data was transferred to an encrypted file on the secure university H drive, and the file was deleted from the audio device once the interviews were transcribed. All personal data was encrypted and stored on the researchers' university laptop and university desktop computer (see *section 3.6* for data storage and confidentiality).

3.5.3.3 Data Triangulation

Denzin in the 1970s introduced the notion of triangulation into qualitative research as a strategy of validation (Denzin 1978). In later research, Denzin approaches triangulation as a strategy for "*broader, deeper, and more comprehensive understandings*" of the subject area being studied and therefore a step towards more knowledge, which can include discrepancies and contradictions in the findings (Denzin 1989; Uwe Flick 2009). The concept of triangulation holds that a research problem is made up of at least two types of methods or perspectives (Uwe Flick 2009). The results of the questionnaires and the findings of the interviews were triangulated to create a more comprehensive picture of the factors that influence adherence to oral chemotherapy medicines. Yin (2017) argues that case study researchers who use multiple sources of evidence are more likely to have accurate and convincing findings in their research. In this study, for example, the BMQ questionnaire data found that beliefs in

treatment necessity outweighed treatment concerns. This was reinforced by the interview findings, which included the participants' determination to necessitate oral chemotherapy therapy to stay alive and fulfil their family responsibilities. By triangulating the forms of evidence, the dependability of the case study findings was further strengthened. The different sources of evidence provide numerous measures of the same case that would ultimately increase confidence that the case study had suitably interpreted the event.

3.5.3.4 Challenges with Data Collection

When conducting real-world research, there are several unexpected challenges, and the researcher's ability to control the nature of such research is limited. This section details some of the difficulties encountered during the study and explains why certain aspects of the study had to be changed.

Observational Data

Participant observation was originally intended to be used as a research method to gain a better understanding of colorectal cancer patients' adherence behaviours and interactions with clinicians during medical consultations. The idea was for the researcher to gain insight into how CRC patients engage with their clinician in their natural environment when discussing medication adherence issues. However, an important aspect of observational research is the data collected in field notes, and the quality of the research is dependent on it.

According to Spradley (1980), when researchers are collecting data in the field, there are three principles that need to be taken into account: the *language identification principle*, the *verbatim principle*, and the *concrete principle*. At the point of collecting data, the researcher was not able to adhere to two of the principles due to unforeseen circumstances. The '*Verbatim principle*' states that the researcher must record what people say verbatim rather than translating it into another format, as this can affect the meaning and context of the dialogue (Spradley, 1980). Using an audio device in consented situations is one way to ensure that all information is captured; however, due to the sensitive and confidential nature of the conversations, the researcher did not obtain permission from healthcare providers to record the events. As medical consultations were bespoke and only lasted for approximately 10-15 minutes, the researcher's ability to record conversations verbatim was limited. In all forms of investigation, the researcher's principles will not always correspond to those of the participants (clinician and/or patient), who have their own personal concerns, values, and interests that should be respected and considered first. The '*Concrete principle*' maintains that the researcher should use concrete language when describing observations (Spradley, 1980). In addition, generalisations should be avoided in field notes to give the exploratory study more depth. However, due to the brief consultation sessions, there was limited discussion about medication use, and the researcher was unable to fully explain and depict the situation. As a result, it was decided to use the observational sessions to build a patient profile, and notes were taken to inform the interviews. For example, notes were made of any topics of interest raised relating to the oral chemotherapy medication that could be discussed in greater detail during the interviews, such as side effects, dose changes, and so on.

Recruitment of Participants

Unfortunately, due to the ongoing coronavirus outbreak, recruitment of new patients and researcher attendance at clinics were abruptly terminated as of 2nd March 2020. It was initially assumed there would be a pause before data collection resumed, and as such, my letter of access from Velindre R&D was extended to reflect the interruption in data collection. However, due to the rapid spread of the virus, it became evident that it would be impossible to continue. After consulting with the supervisory team, it was decided that the researcher would continue with telephone interviews and finish the questionnaire analysis as there was a sufficient number of participants (n=59) for the first unit of analysis.

3.5.4 Data Analysis Procedure

3.5.4.1 Quantitative Unit of Analysis 1

Participants completed paper-based questionnaires, which were then entered into the Online Surveys database (formerly Bristol Online Surveys) (<https://www.onlinesurveys.ac.uk/>), an online web service for developing and analysing surveys. The response data from the online surveys' dataset was also exported into SPSS version 23.0 for frequency distributions. Before inputting the data, possible errors were checked against the questionnaire, and corrections were made as needed. Two pieces of missing data arose from the questionnaires that were completed at home (one missing DOB and one missing answer in the BMQ questionnaire). On each occasion, the researcher promptly analysed them for any errors, and the questions were discussed with the participant while they were at the clinic to rectify the information.

The MARS scores for each item were summed to give a total score ranging from 8 to 40, with higher scores indicating higher levels of reported adherence. Due to the negatively skewed results, adherence was measured using a dichotomous scale and classified as adherent (MARS=40) and non-adherent (MARS<40). Response categories were rated on a 5-point Likert scale (*never (5), rarely (4), sometimes (3), often (2), and very often (1)*) (Horne and Weinman 2002). The adherence score gives an indication of participants standing on a certain aspect of adherence rather than a precise indicator of when and how they took their oral chemotherapy medicine. The researcher presented the MARS tool to participants in such a way that it was clear that it solely considered their oral chemotherapy drug.

The BMQ questionnaire consisted of a pool of 18 statements representing commonly held beliefs about treatment necessity (BMQ-N; five items), treatment concerns (BMQ-C; five items) and general medication beliefs (BMQ-G; eight items) (Horne and Weinman 1999). BMQ-N examines the beliefs of necessity towards a specific medication, in this case oral chemotherapy medicines, while the BMQ-C examines concerns about the negative effects of the medication. The BMQ-G assesses beliefs about medicines in general, corresponding to the themes of general overuse (four items) and general harm (four items). The statements have response categories rated on a 5-point Likert scale (*strongly disagree (1), disagree (2), uncertain (3), agree (4) and strongly agree (5)*). Higher scores (above the midpoint) indicate stronger beliefs in the concepts represented by the scale. The BMQ-N and BMQ-C subscales, for example, ranged from 5 to 25, with scores above 12.5 indicating strong beliefs.

3.5.4.1.1 Welsh Index of Multiple Deprivation (WIMD)

The Welsh Index of Multiple Deprivation (WIMD) is the official measure of relative deprivation for small areas in Wales (Welsh Government, 2014). The WIMD identifies areas with the highest concentrations of deprivation, which are comprised of eight main types of deprivation, including: income, employment, health, education, access to services, housing, community safety, and the physical environment (Welsh Government, 2014). Multiple deprivation incorporates more than one of these variables being experienced by a concentration of individuals in a given area, and WIMD quartiles rank all small areas in Wales from 1 (the most deprived) to 4 (the least deprived). The WIMD analysis aimed to determine whether MARS adherence scores were related to multiple levels of deprivation in South Wales. The WIMD's postcode lookup spreadsheet is available on a publicly accessible website. The participants postcodes were coded on the spreadsheet, and a quartile ranking score obtained. The participants MARS adherence scores were categorised according to the WIMD data ranking as a descriptive scale ranging from the most deprived areas to the least deprived (1-4). Correlation analysis was conducted on SPSS using Pearson's chi-squared analysis to determine whether there was a significant association between MARS sum scores and WIMD deprivation quartiles.

3.5.4.2 Qualitative Unit of Analysis 2

The framework method was used for the management and analysis of the qualitative data based on Gale et al. (2013) and its additional file. The method, which is increasingly being applied in medical and health research, began in the late 1980s in social policy research and

was further developed by Jane Ritchie and Liz Spencer of the National Centre for Social Research's Qualitative Research Unit (Ritchie and Lewis, 2003). The framework method of analysis is a form of thematic analysis that aims to identify commonalities and differences in qualitative data. It then focuses on the relationships between different parts of the data, seeking to draw descriptive and/or explanatory conclusions based on themes (Gale et al. 2013). In applying this form of analysis, a broadly deductive approach was applied from the existing theoretical proposition (WHO, 2003) and open coding of any issues that did not fit the framework. Regular meetings with the research supervisory team were arranged that helped bring all our perspectives together for discussion. Participant transcripts were analysed until we reached an agreement and thus established decisions on the themes and categories to which they fit. The steps involved in each of the seven stages of framework analysis are detailed below. For examples of the framework method used for analysing qualitative data and a brief description of its development, please see *Appendix 9*.

3.5.4.2.1 Framework Method of Analysis of Qualitative Data

Stage 1: Transcription

The researcher was responsible for conducting participant interviews, transcribing them verbatim, and ensuring that the transcription styles were consistent. Interviews were all transcribed verbatim by the researcher in order to immerse himself in the data. There were 16 interviews lasting between 21 and 52 minutes, with a mean length of the interviews of approximately 35 minutes. Each transcript was reviewed for formatting inconsistencies and grammatical errors, as well as to ensure that the data was anonymised to remove any personally identifiable information. Early in the transcription process, both members of the

supervisory team (JH and MC) examined select transcripts to ensure that the formatting was consistent, and any flaws were corrected. As with the framework method, the researcher was interested in the content, so only long periods of silence or pauses in the interview, intermissions, and nonverbal communications (such as crying or laughter) were noted in the text (Gale et al. 2013). After completing the transcription, the researcher double-checked all the transcripts by listening to the audio recordings again while simultaneously reading the transcripts to look for any human errors.

Stage 2: Familiarisation with the interview

The researcher became familiar with all of the interviews, while the supervisory team became familiar with the assigned interviews, which were chosen because of the depth of wide-ranging topics discussed by the participants, which provided a broad perspective. While doing so, the researcher kept track of any early thoughts, noting any particularly strong or opposing viewpoints. One participant, for example, expressed strong emotion (frustration), as he recalled his dislike for taking the oral chemotherapy medication due to ongoing side effects and events that hampered his mobility. The researcher was able to navigate through all of the transcript documents more easily after familiarising himself by reading and taking notes in this manner.

Stage 3: Coding Process

The researcher met with his supervisory team to discuss the approach to the analysis work. It was agreed that the researcher would create an initial analytical framework to provide structure and be used to manage and organise the data that could help answer the research question. The researcher opted to further his coding knowledge and skills by completing an

online e-learning module on coding qualitative data. This improved both the researcher's coding confidence and refined his technique for capturing a code within textual data. The researcher also acknowledged that he needed to distinguish between codes derived from the literature and those derived from his own interpretation of the data.

An initial analytical framework based on the WHO framework (WHO, 2003) was developed, and codes were identified as a result of this, as well as familiarisation with the transcript data. Particular attention was given to the research question and how it informed my critical thinking. The initial analytical framework included brief descriptions of each individual code to maintain consistency with the coding process. At this stage, the researcher and one supervisory member independently coded an assigned transcript according to the initial analytical framework and open codes for segments that did not fit the framework. Interesting segments of the text were underlined, and the transcripts were printed with large margins.

Stage 4: Developing a working analytical framework

After the researcher and supervisory team had coded the transcript, we reconvened to discuss the codes and labels assigned to each passage. The transcript was analysed to establish differences in interpretation of the data, its significance to the research question, and its relation to the participants' views on the factors influencing adherence to oral chemotherapy at home. By comparing and contrasting each other's notes and codes, the level of coding agreement between the research team was assessed, as was whether to introduce new codes to the initial analytical framework. After reaching an agreement, the researcher coded the remaining transcripts independently, applying the updated analytical framework,

while simultaneously noting any new codes or impressions that did not fit the existing analytical framework.

The analytical framework was reviewed again to integrate new and refined codes after the researcher had coded the remaining transcripts. At this stage, we discussed whether some codes were conceptually related and therefore grouped together to form overarching categories. The process of refining, applying, and refining the analytical framework was repeated until no new codes were produced. The final analytical framework was made up of five main themes and twenty-four codes grouped into twelve categories (see *Table 5.2*).

Stage 5: Applying the analytical framework

The researcher systematically went through each transcript, highlighting meaningful passages of text, and selecting and attaching an appropriate code using the final analytical framework. Comments were added to the Review tab in Microsoft Word by selecting 'New Comment' and attaching the appropriate code from the final analytical framework. These comments appear in a balloon in the document's margin. *DocTools* was then used to extract the textual data and corresponding codes into a separate Word document in a tabular format. After reviewing various analytical tools that were available, e.g., SPSS, I found the *DocTools* package was best suited for my analysis in obtaining the relevant information from the original participant transcript (<https://www.thedoctools.com/home/en/front-page/>). The *DocTools* software was downloaded onto Microsoft Word as an add-in plug because of its compatibility with the Microsoft software. The Microsoft Word Add-in enabled the researcher to extract the page number, line number, textual data to which the code related, the original codes, and the author.

Stage 6: Charting data into the framework matrix

Figure 3.2 Charting data into the framework matrix: a segment from theme one (patient-related factors) illustrating categories (grey) and codes with verbatim quotes.

Participants	Oral Chemotherapy - Dosing Regimen	Following Instructions	Routine	Adverse Effects of the Treatment	Side Effects
P000004		"I go to the doctors, and they explain everything to me about it. About what I got to take and what treatment I'm on and they explain it all to me down there"(pg.3), "What they tell me to do I would follow"(pg.3)			<i>tiredness</i> - "It affects your social life because you're so tired"(pg.2), "...feeling tired 24/7."(pg.8); <i>Vomiting</i> - "I would vomit for a day or maybe two after that treatment with the tablets"(pg.9); <i>Infections</i> - "I used to pick up an infection often...kept giving me infections I used to go in there every 6-7 weeks I used to end up back in hospital having treatment for infections."(pg.9)
P000006		"I was given the amount of tablets to take for the next two weeks which I stuck to rigidly."(pg.3), "I was doing as I was told"(pg.5)	"You know you got to take these things, so you get into a routine then."(pg.4)		
P000011					<i>Hand-foot syndrome</i> - "I told them I was feeling numbness in my fingertips."(pg.2); <i>Taste (film-coating)</i> - "...the main one for me is the taste. You lose your taste. Everything tastes bland and not particularly nice."(pg.7), "I am eating it's just disappointing when I do eat. It doesn't taste like how I expect it to"(pg.7); <i>Tiredness (fatigue)</i> - "...the fatigue after 4-5 days after treatment that's when I start to get tired."(pg.7)
P000012		<i>12-hour interval</i> - "say I woke at 9 o'clock in the morning I would take it 6 o'clock at night. I tried to get it in that habit if you know what I mean between 9 and 10 hours after the first one because otherwise you take it late at night "(pg.5)	"they've given you a routine to take it – you've got to have a routine!"(pg.13)		<i>Hand-foot syndrome</i> - "...the treatment has left me with numb hands and feet"(pg.2); <i>Diarrhoea</i> - "...it was making me quite ill like diarrhoea which was one of the worst things that was happening"(pg.2)

At this stage, the verbatim quotes were charted in a spreadsheet matrix using Microsoft Excel, and a separate tab was created for each theme (see *figure 3.2*). *DocTools* was useful for

transferring the extracted data since it allowed for easy examination of the data and was effective in identifying interesting codes that were mapped into the framework matrix. The framework matrix had one row for each interview with a participant and one column for each code that was grouped together by category.

Stage 7: Interpreting the data

During the interpretation phase, the researcher dug deeper into the data analysis, looking for emerging patterns that could explain the 'case' (adherence to oral chemotherapy medicines) beyond the individual participant reports. Themes were initially applied from the existing theoretical framework of the five dimensions of adherence (WHO, 2003). By making connections within and between participant interviews, the data set was meticulously analysed for emerging themes. Through checkpoint meetings with the research team, ideas were generated, explored, and reviewed. This process was influenced by the objectives of the research as well as new categories and codes generated inductively from the research. This was important for following up on emerging connections as well as removing points that did not align with the research objectives.

3.5.5 Quality in Qualitative Research

Approaches to qualitative inquiry have become more diverse, including work informed by philosophical and theoretical assumptions, raising issues about the quality and trustworthiness of the research (Patton, 1999). Demonstrating the quality of research has proven difficult for qualitative researchers. Lincoln and Guba (1985) argue that constructivists

require a criterion for evaluating research, and they propose four important principles for assessing the quality of qualitative research: credibility, transferability, dependability, and confirmability. Yin (2017), on the other hand, suggests construct validity, external validity, and reliability tests to determine the quality of exploratory social science research. However, most qualitative researchers agree that the criteria used by quantitative researchers associated with reliability and validity are not conducive to qualitative studies. In this section, the criteria for assessing the quality of this research, proposed by Guba and Lincoln (1985), will be addressed.

3.5.5.1 Credibility

Credibility is seen as one of the most important factors in determining the trustworthiness of a study (Patton, 1999). It is said to be established when the research findings demonstrate the truth of the study findings and have a fundamental appreciation of the naturalistic inquiry. According to Lincoln and Guba (1985), data triangulation, member checking with participants to understand whether the findings reflect their experiences, and peer debriefing with other researchers can all help to improve credibility.

Through the data triangulation in this study, the researcher was able to analyse the data and develop a deeper and more thorough understanding of the phenomenon. In addition, during the interviews, the line of inquiry was prompted on multiple occasions and approached in different ways to ensure there was agreement between the participants' beliefs and experiences and the way in which the researcher interpreted their viewpoints. Throughout the study, the researcher was overseen by two supervisors for peer debriefing with regular, in-depth conversations. This allowed for new perspectives to be considered as well as for the

researcher to reflect on how the findings were interpreted. A peer debrief was also helpful at several stages of the research, including the research design, philosophical opinions, data collection, and ethical considerations.

3.5.5.2 Transferability

The extent to which study findings can be applied in various contexts and investigations is referred to as transferability. As a result, it is equivalent to generalisability or external validity. Yin (2017) states that for case studies, the external validity challenges arising from the original research question posed do not relate to statistical generalisation. Rather, as Hammersley (1992) describes, the context in which generalisation is discussed is theory building, and it incorporates notions or propositions that are thought to have a broader application. Likewise, this study produced an in-depth analysis of the complexity of adherence decision-making among colorectal cancer participants receiving oral chemotherapy treatment, which may be transferable to other cohorts.

3.5.5.3 Dependability

Dependability refers to the consistency of the results and is similar to the concept of reliability in quantitative research. Lincoln and Guba (1985) approach this concept by asking whether similar findings would be produced if another researcher were to undertake the research. To address the study's dependability issues, the methodological approach provides an audit trail that includes detailed descriptions of the methodologies, recruitment procedures, data analysis, and ethical considerations. Furthermore, data triangulation was carried out, as well

as peer debriefings with two supervising researchers at each stage of the data analysis until an agreement was reached.

3.5.5.4 Confirmability

This study was guided by the use of a research protocol that was created to organise and carry out the study, and as a result, it has an audit trail that can be used to assess the confirmability of the findings. Furthermore, when determining the quality of research, Ritchie and Lewis (2003) argue that the researcher should make their assumptions clear as they can have an influence on data collection and analysis. Reflexivity on the part of the researcher openly acknowledges their influence on the study and is addressed below.

3.5.5.5 Reflexivity

Qualitative research is inherently subjective, as it represents, in this case, one researcher's interpretation of the subject under study. It is acknowledged that the researcher plays an important role in any construction of knowledge. As a result, it is critical for the researcher to understand their involvement in the research process and how it may have influenced data collection and analysis. Constructivists assert that reality is subjective since it is derived from the individual viewpoints of the study's participants and is, thus, multiple and varied (Adom et al. 2016). This understanding helps in addressing the power relations between the researcher and the participants because it clarifies that the researcher's role in data analysis and their expertise do not in any way confer dominance, or the authority to form a judgmental analysis (Karnieli-Miller et al. 2009). The researcher concedes that his interpretation of the data was influenced by his pharmacy background and that he had no personal experience

with colorectal cancer or a family history of the disease. At its core, the study was an exploration of what South Wales residents with colorectal cancer reported to a male researcher, about the factors influencing their adherence to oral chemotherapy medicines.

In constructivist paradigm data analysis, the researcher should be cautious when they are constructing a picture of the phenomenon that takes shape as they collect and examine the parts of the data collected (Adom et al. 2016). Therefore, the researcher reflects continuously on how their own actions, values, and perceptions impact the research setting as they construct meanings that clearly paint the true state of the phenomenon studied. Before collecting data, the researcher explored the conceptual issues of adherence and conducted a literature review of the factors influencing CRC patients' adherence to oral chemotherapy medicines, which offered an insight into the research topic from which theoretical propositions were derived. Furthermore, the researcher acknowledges that the influence they have through their interactions with participants, in varying degrees, can impact the research, e.g., the interview process. The researcher must ensure that each participant has the right and ability to object (Brinkmann and Kvale 2005). In relation to this study, the researcher knew not to divulge personal information about themselves and was trained to some extent to use open, non-leading questioning techniques. It is acknowledged that there is potential for the researcher to hear information from the participants about difficult emotional moments of their lives relating to their treatment or CRC diagnosis. Consequently, the researcher has not only an ethical but also a professional responsibility to ensure that data and findings are not just treated confidentially and presented with sensitivity but also that participants are reassured about the nature of the study and its dissemination.

Language is an important aspect of socially construed knowledge, meaning that the same event can be described and understood in different ways (Guba & Lincoln 1994). The researcher was mindful of his positionality in the choice of language used during data collection and how this may affect the research. Furthermore, in order to avoid simply expressing the researcher's viewpoints, the interpretation of the findings was grounded in participant accounts. The awareness of such implications enabled the researcher to reflect upon these factors and ensure that he was responsive and reflective about research decisions.

3.6 Data Management and Confidentiality

The confidentiality and privacy of participants and healthcare providers were respected throughout the study, and it was taken with the utmost responsibility to ensure that all records and conversations were kept in this manner. Personal data confidentiality was handled in accordance with the Data Protection Act of 2018. The researcher also followed the data confidentiality protocols and guidelines established by Velindre University NHS Trust and Cardiff University, respectively. If assistance was required, the university's Data Protection Officer, based in the Governance and Compliance Division, was available.

Participants in the survey were asked to provide sociodemographic information but not any information that might be used to identify them. To protect participant anonymity, all participant identifying information was anonymised, and each was assigned a unique six-digit participant identification number. Only with the written consent of each participant was an audio recorder used during the interviews to ensure they were comfortable with its presence. Furthermore, the researcher had transcribed all the interviews verbatim in order to immerse

himself in the data. During the transcription process, each transcript was reviewed by the researcher to ensure that all personally identifiable data was anonymised to preserve confidentiality. Once the interviews were transcribed, the data was transferred to an encrypted file on the university's secure H drive, and the file was deleted from the audio device.

The research site file, which contained all the essential documentation, was kept up to date as recommended by Health and Care Research Wales. Personal identifiable data, for example, from consent forms, was stored separately from the research documentation data. Personal addresses, postcodes, emails, and phone numbers were only used to contact the participant by the researcher. Furthermore, all electronic data collected was saved to an encrypted folder on the researcher's laptop and backed up using the university's secure "H" drive, which was password protected. Paper documentation was kept in a folder and securely locked on the university grounds at Eastgate House. Only authorised personnel were provided access to the data files, which included the researcher and academic supervisors. Entrance to Eastgate House requires university identification at both the main building entrance and the 12th floor.

3.7 Ethical Considerations

All practical efforts were taken to ensure that interested participants could take part in the research. The English language is the most commonly spoken language in South East Wales. The researcher is also an English speaker and does not speak the Welsh language. The material in the patient information sheet had been produced to an easy-to-read standard with short sentences, wordings, and paragraphs. If the participant spoke Welsh, Velindre University NHS Trust had a Welsh language facility dedicated to providing bilingual care to

patients. The interviews, however, were conducted in English to gain a deeper understanding of medication adherence and influencing factors to oral chemotherapy agents. While this study strives to include all patients, it was necessary for eligible participants to be able to read and respond in English.

3.7.1 Valid Informed Consent

The researcher had completed training in both valid informed consent and good clinical practice through Health and Care Research Wales. The training provided the researcher with the tools needed to ensure that participants were well informed and that all of their questions were appropriately answered. The researcher understood that participants should not be rushed into making a decision and, where possible, should be able to confide in family, friends, and other healthcare members. The study was entirely voluntary; therefore, participants were encouraged to take as much time as needed to make an informed decision on whether to participate. Participants were provided with an information sheet that specified key information about the research. If potential participants showed an interest, the researcher was accessible at the outpatient clinic throughout the morning clinics and through email or telephone, as mentioned to all participants, to provide more detail about the study. Likewise, the researcher explained to the participants that they had the right to withdraw at any point without any ill effect on their medical treatment at Velindre or at any other NHS hospital.

Patients with clear intellectual impairment or capacity were excluded from the study. The researcher followed the principles outlined in the Mental Capacity Act of 2005. Prior

screening was carried out by the researcher based on the feedback received from the healthcare team that had had prior contact with the participant. All patients who were deemed to be without capacity or with obvious learning difficulties by the healthcare team were automatically excluded from the research. The researcher also reaffirmed capacity with all individuals that were approached by briefly discussing with them the nature of the research and confirming they understood. A person must be assumed to have capacity unless it is established that they lack it.

3.7.2 Potential Risks and Burdens

The main burden for the participants was the time commitment to take part in the study and the resultant issues with their work schedules and other commitments, including travel and transportation. Participants were given the option of arranging the interview for a convenient time and bringing along supportive friends or family members. Travel expenses were made available with funding from the KESS2 scholarship budget for participants that travelled to the Eastgate House or the outpatient clinic for a pre-arranged interview. Furthermore, Richardson et al.'s (1998) article describing the recruitment experience of a complementary alternative medicine trial after breast cancer found that one of the primary reasons for non-participation was lack of interest (24%), for reasons such as wanting to forget their illness and conflict with religious beliefs. In the initial approach, healthcare clinicians were aware that they should recommend only interested participants to the researcher. Additionally, the researcher was mindful in his approach to ensure participants had the necessary time to make an informed decision as stated above (3.6.1) and that they had the freedom to withdraw consent at any moment without having to give a reason.

The main burden for the specialist colorectal clinicians was also their time spent identifying and approaching study participants during morning clinics. There were no anticipated risks to the healthcare team during the course of data collection for the research. However, if unethical practises were identified or there were patient safety concerns, such as a breach of information containing patient identifiable details, the researcher understood that it needed to be addressed as soon as possible. In the event of a data breach, the relevant person and authorities were to be informed in accordance with Velindre University NHS Trust and Cardiff University policies.

3.8 Research Ethics Committee and Approvals

This study was assessed and approved by both the NHS Research Ethics Committee and Health and Care Research Wales (HCRW). The North of Scotland Research Ethics Committee (1) approved the study on July 9th, 2019 (REC reference: 19/NS/0121). Approval from HCRW was received on July 11th, 2019. Furthermore, a letter of access to conduct research at Velindre University NHS Trust was received on July 12th, 2019.

Chapter Four

Results: Unit of Analysis 1

4.1 Introduction

This chapter provides details of the first phase of the study. The following objectives were addressed in this subunit of analysis:

- Assess sociodemographic status and patient adherence to medication using the Medication Adherence Report Scale (MARS).
- Examine patients' beliefs about treatment influence (necessity and concerns) and commonly held beliefs about medication using the Beliefs about Medicines questionnaire (BMQ).

This chapter begins with an overview of the participation rates of patients with CRC receiving oral chemotherapy treatment from a single outpatient clinic. The chapter then presents the survey results from the first unit of analysis as part of an embedded case study exploring factors influencing patient adherence to oral chemotherapy medicines. This unit of analysis includes three separate sections: the sociodemographic characteristics of participants; assessing medication adherence using the MARS scale; and participants' beliefs about medication using the BMQ.

4.2 Participation

Data was collected over an eight-month period, from July 15th, 2019, to March 2nd, 2020. Participants were recruited from 41 clinic sessions, and 108 patients who met the inclusion criteria were scheduled for outpatient clinic appointments during this time period. At the clinic sessions, 22 patients were deemed unsuitable due to experiencing complications in their treatment and therefore were not approached to take part.

Of the 86 patients that were invited to take part in the study, 73 (84.9%) individuals demonstrated interest in the study and were provided further details. Fifty-seven (66.3%) participants completed the survey onsite at the outpatient clinic. Thirteen (15.1%) individuals declined interest in the study, and 16 (18%) agreed to complete the survey at home. Eleven (12.8%) either misplaced or did not return the survey. Seven (8.1%) participants had returned the questionnaire to the researcher or a clinician at the clinic. Of these, 2 (2.3%) were followed up on to collect missing or incomplete data. In total, 59 participants (68.6%) had completed questionnaire surveys. The majority (n = 57, 66.3%) of the questionnaires were completed onsite at the outpatient clinic, and this made the process of detection straightforward as the researcher was able to verify any ambiguous answers with the participant.

4.3 Sociodemographic Characteristics

The sociodemographic characteristics, cancer diagnosis, current oral chemotherapy medication prescribed, and total number of prescribed medications are presented in *Table 4.1*.

Table 4.1 Sociodemographic characteristics.

Participant Characteristics	Participants (N)	Percent (%)
Gender:		
Male	35	59.3
Female	24	40.7
Age:		
41-50	4	6.8
51-60	15	25.4
61-70	18	30.5
71-80	21	35.6
81-90	1	1.7
Mean = 65.7		
SD = 10.2		
Range = 42-82		
Cancer Diagnosis:		
Colon	33	55.9
Rectal	26	44.1
Prescribed Oral Chemotherapy medication:		
Capecitabine (Xeloda®)	57	96.6
Trifluridine + Tipiracil (Lonsurf®)	2	3.4
No. of prescribed medication(s)		
1	15	25.4
2	10	16.9
3	8	13.6
4	10	16.9
5	4	6.8
6 or more	12	20.3
Mean = 3.2		
SD = 1.9		
Ethnicity:		
White	59	100
Marital Status:		
Single	11	18.6
Married	36	61
Widowed	3	5.1
Divorced	8	13.6
Separated	1	1.7
Area of Residence:		
Blaenau Gwent	1	1.7
Bridgend	12	20.3
Caerphilly	15	25.4
Cardiff	6	10.2
Merthyr Tydfil	1	1.7
Monmouthshire	1	1.7
Newport	11	18.6
Rhondda Cynon Taff	3	5.1
Torfaen	6	10.2
Vale of Glamorgan	3	5.1
Education:		
1 or more GCSE'S	9	15.3
1 or more O Levels/A-Levels	10	16.9
Professional Diploma or equivalent	13	22
Bachelor's Degree	5	8.5

Master's Degree	2	3.4
Doctorate/PhD	2	3.4
No Qualifications	17	28.8
Other	1	1.7
Employment Status:		
Employed	13	22
Self-employed	1	1.7
Not in Work	2	2
Student	0	0
Retired	36	61
Unable to Work	7	11.9
Prefer not to say	0	0
Welsh Index of Multiple Deprivation (WIMD)*		
Quartile 1 - Most deprived	15	25.4
Quartile 2	15	25.4
Quartile 3	10	17
Quartile 4 – Least deprived	19	32.2

*Data was taken from the Welsh Statistics 2011 census as no data was available on the NHS Wales database.

The mean age of participants was 65.7 years (SD = 10.2, range = 42-82), with the highest cohort (35.6%, n = 21) aged between 71 and 80 years old. Most of the participants had either retired (61%, n = 36) or were unable to work (11.9%, n = 7), compared to 23.7% (n = 14) who were either employed or self-employed. The marital status of most participants (61%, n = 36) was married, while 18.6% (n = 11) were single, and 20.4% were either divorced (n = 8), widowed (n = 3) or separated (n = 1). Additionally, over a third of participants (37.3%, n = 22) held a professional diploma (equivalent) or above; however, 28.8% (n = 17) had no qualifications, 16.9% (n = 10) had 1 or more A-Levels, and 15.3% (n = 9) had 1 or more GCSEs.

The data obtained from the 2011 Welsh census identifying the WIMD of relative deprivation revealed a roughly equal representation from each quartile, with 50.8% (n = 30) of participants living in an area considered to be in the two highest quartiles (1 and 2) for the most deprived, compared to 49.2% (n = 29) in the quartiles (3 and 4), indicating the least deprived.

The type of colorectal cancer treated with oral chemotherapy medication revealed that over half the participants were diagnosed with colon cancer (55.9%, n = 33) and rectal cancer in (44.1%, n = 26). The mean number of total prescribed medications was 3.2 (SD = 1.9) of which a quarter of the participants (25.4%) stated they were only prescribed a single medication. The most common oral chemotherapy medication prescribed to participants was Capecitabine (Xeloda®), with only 3.4% (n = 2) reporting Trifluridine + Tipiracil (Lonsurf®).

4.4 Medication Adherence Report Scales (MARS)

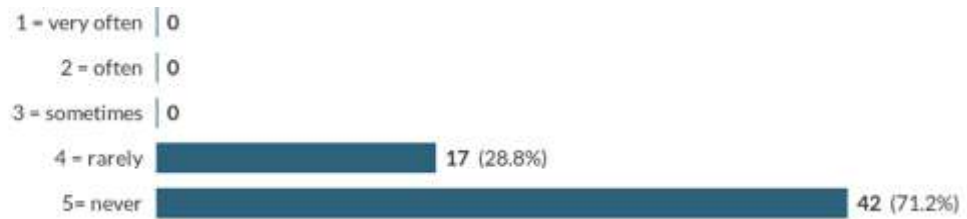
Table 4.2 Description of the Medication Adherence Report Scale (MARS-8) and its Individual Items.

MARS Item	Mean (SD)	Median	Item Range
I only use my (*name of medicine*) when I need it	4.8 (0.89)	5	1-5
I decide to miss out a dose	4.9 (0.36)	5	1-5
I try to avoid using it	5 (0)	5	1-5
I forget to take it	4.71 (0.46)	5	1-5
I alter the dose	5 (0)	5	1-5
I stop taking it for a while	5 (0)	5	1-5
I use it as a reserve, if my other treatment doesn't work	5 (0)	5	1-5
I take it less than instructed	5 (0)	5	1-5
Sum Score MARS-8*	39.41 (1.07)	40	8-40

*The MARS-8 sum score was calculated by summing scores from each individual item (range = 1-5). Higher scores indicate higher self-reported adherence with a maximum score of 40.

The MARS-8 sum score was calculated for all participants who had completed responses to the survey. During the studied period, the mean and median adherence scores were 39.41 (98.5%) and 40 (100%), respectively. Almost two-thirds of the participants (64.4%, n = 38) were classified as adherent with a MARS score of 40 (100%). Nonetheless, in 30.5% (n = 18) of respondents, the MARS score was between $\geq 95\%$ - $< 100\%$ (score of 39 or less) and in 5.1% (n=3) the MARS score was $\leq 90\%$ (score of 36 or less). The percentage of participants that were non-adherent to one or more of the eight MARS statements was 35.6% (n = 21).

Figure 4.1 – Bar chart illustration of the MARS item - “I forget to take it”.



The most common statement (shown in figure 4.1) was “I forget to take it” with 28.8% (n = 17) of participants reporting that the statement applies to them on ‘rare’ occasions. The mean adherence rank for the statement was 4.71 (SD = 0.46) with a variance of 0.21. When comparing the highest and lowest category of WIMD deprivation for this MARS statement (33% in quartile 1 compared to 21% in quartile 4), there is a 12% difference in the report of forgetfulness. However, the study’s sample size was too small for any meaningful statistical analysis. Nevertheless, five of the participants who, on the rare occasions, experienced forgetfulness agreed to an interview to discuss their adherence to the medication in more detail.

Figure 4.2 – Bar chart illustration of the MARS item - “I decide to miss out a dose”.



The MARS statement (shown in Figure 4.2) “I decide to miss out a dose” reported an adherence score of 91.5% (n = 54) though 8.5% (n = 5) were not fully adherent. The mean adherence rank for deciding to miss a dose was 4.9 (SD = 0.36) with a variance of 0.13. Of the

participants that were not fully adherent, 6.8% (n = 4) reported that the statement applied to them on a 'rare' occasion, and 1.7% (n = 1) specified that he 'sometimes' decided to miss a dose of medication. Additionally, 5.1% (n = 3) of participants who said they would miss a dose on the "rare" occasion were also more likely to forget to take their medication on the "rare" occasion.

Figure 4.3 – Bar chart illustration of the MARS item- *"I only use my (*name of medicine*) when I need it"*.



The MARS statement (shown in Figure 4.3) *"I only use my (*name of medicine*) when I need it"* showed a MARS score of 94.9% (n = 56). The mean adherence rank for this item only was 4.8 (SD = 0.89) with a variance of 0.77. Of the 5.1% (n = 3) participants who were non-adherent, 3.4% (n = 2) were adherent to all other MARS statements, and one participant (1.7%) reported forgetting to take their medication on the 'rare' occasion.

4.4.1 WIMD Deprivation Scales and Medication Adherence Rate

The medication adherence rate is summarised below *Table 4.3* according to the WIMD data ranking from the most deprived areas to the least deprived (1-4) as a scale descriptive. The

mean, standard deviation, median distributions of participants are presented, as well as those achieving a MARS-8 sum adherence score of 40 (100%) for each quartile.

Table 4.3 Description of MARS-8 and WIMD deprivation quartiles (1-4) crosstabulation.

WIMD Quartile*	Number of Participants (n=59)	MARS-8 Mean Score (SD)	Mars-8 Median Score	No. of Adherent Participants (MARS = 40)
Quartile 1 – most deprived	15	39.07 (1.39)	40	8 (53.3)
Quartile 2	15	39.47 (1.06)	40	10 (66.7)
Quartile 3	10	39.50 (0.71)	40	6 (60)
Quartile 4 – least deprived	19	39.58 (0.96)	40	14 (73.7)

*Data was taken from the Welsh Statistics 2011 census as no data was available on the NHS Wales database.

Figure 4.4 – WIMD Quartiles Crosstabulation and MARS-8 scores.

WIMD 2019 * total Crosstabulation								
			MARS-8 total scores					Total
			35	36	38	39	40	
WIMD Quartiles	1	Count	1	0	3	3	8	15
		%	6.7%	0.0%	20.0%	20.0%	53.3%	100.0%
	2	Count	0	1	0	4	10	15
		%	0.0%	6.7%	0.0%	26.7%	66.7%	100.0%
	3	Count	0	0	1	3	6	10
		%	0.0%	0.0%	10.0%	30.0%	60.0%	100.0%
	4	Count	0	1	0	4	14	19
		%	0.0%	5.3%	0.0%	21.1%	73.7%	100.0%
Total		Count	1	2	4	14	38	59
		%	1.7%	3.4%	6.8%	23.7%	64.4%	100.0%

Figure 4.5 – WIMD deprivation categories and MARS-8 scores

Symmetric Measures					
		Value	Asymptotic Standardized Error ^a	Approximate T ^b	Approximate Significance
Interval by Interval	Pearson's R	.170	.131	1.303	.198 ^c
Ordinal by Ordinal	Spearman Correlation	.174	.130	1.330	.189 ^c
N of Valid Cases		59			

- a. Not assuming the null hypothesis.
- b. Using the asymptotic standard error assuming the null hypothesis.
- c. Based on normal approximation.

The data analysis found no significant relationship between WIMD categories of deprivation and medication adherence scores (as shown in *figures 4.4 and 4.5*). This is likely because the MARS scale does not discriminate between those with high and low adherence scores; hence, the scale was incapable of capturing differences in adherence to oral chemotherapy agents. Nevertheless, the WIMD data indicated that just over half (53.3%, n = 8) of participants living in the most deprived areas (Quartile 1) were adherent, achieving a MARS score of 40. In addition, 73.7% (n = 14) of participants living in the least-deprived areas (Quartile 4) were adherent. Comparing the least and most deprived areas, the chi squared test of independence indicated a statistically significant ($p = 0.0002$) difference in adherence between quartile 1 (8/15, 53.3%) and quartile 4 (14/19, 73.7%). However, to support these preliminary results, further research with a larger sample testing the ability of the MARS items to discriminate across WIMD categories would enable a more robust statistical analysis.

4.5 Beliefs about Medicines Questionnaire (BMQ)

4.5.1 BMQ – Necessity and Concerns Subscales (BMQ-N and BMQ-C)

The distribution of participants' responses to the necessity and concern subscales is summarised in *Table 4.4*. Responses to each statement were scored on a 5-point Likert scale (where 1 = strongly disagree, 2 = disagree, 3 = uncertain, 4 = agree, and 5 = strongly agree). The descriptive statistics for all BMQ scales are shown in *Table 4.5*.

Table 4.4 Beliefs about Medicines Questionnaire (BMQ-N and BMQ-C) with mean and standard deviation (SD) values.

	Number (%) of participants						
	Mean	SD	Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
1. BMQ – Specific Necessity Scale (BMQ-N)							
My health, at present, depends on my medicines	3.8	0.8	0	5 (8.5)	11 (18.6)	31 (52.5)	12 (20.3)
My medicines protect me from becoming worse	4.0	0.73	0	3 (5.1)	6 (10.2)	37 (62.7)	13 (22)
My health in the future will depend on my medicines	3.9	0.9	1 (1.7)	5 (8.5)	5 (8.5)	38 (64.4)	10 (16.9)
Without my medicines I would be very ill	3.3	1.0	2 (3.4)	9 (15.3)	25 (42.4)	16 (27.1)	7 (11.9)
My life would be impossible without my medicines	2.9	0.9	2 (3.4)	19 (32.2)	22 (37.3)	13 (22)	3 (5.1)
2. BMQ – Specific Concerns Scale (BMQ-C)							
Having to take medicines worries me	2.4	1.1	9 (15.3)	35 (59.3)	1 (1.7)	11 (18.6)	3 (5.1)
I sometimes worry about the long-term effects of my medicines	2.7	1.2	7 (11.9)	28 (47.5)	5 (8.5)	13 (22)	6 (10.2)
My medicines are a mystery to me	2.8	1.1	4 (6.8)	26 (44.1)	8 (13.6)	18 (30.5)	3 (5.1)
My medicines disrupt my life	2.8	1.2	7 (11.9)	25 (42.4)	3 (5.1)	19 (32.2)	5 (8.5)
I sometimes worry about becoming too dependent on my medicines	2.1	0.8	7 (11.9)	44 (74.6)	3 (5.1)	4 (6.8)	1 (1.7)

Table 4.5 Beliefs about Medicines Questionnaire (BMQ) Scale descriptive

Scale	Number of items in scale	Mean	SD	Number (%) scoring above scale mid-point
Treatment Necessity (BMQ-N)	5	3.59	0.62	55 (93.2)
Treatment Concerns (BMQ-C)	5	2.58	0.72	26 (44.1)

As shown in *Table 4.5*, the number of participants scoring above the scale mid-point for each of the medication belief scales is presented. This provides an indication of the proportion of

individuals holding particularly strong views about the construct being measured by each scale. The scores show that, on average, the participants' belief in the necessity for treatment outweighed their concerns with regard to taking the oral chemotherapy medication.

Of the participants that completed the BMQ survey (n = 59), 93.2% (n = 55) scored over 12.5 for the BMQ-N subscale, indicating strong beliefs in the necessity of the oral chemotherapy medication. While most participants agreed that their oral chemotherapy medication was necessary, 6.8% (n = 4) did not hold this view. On further review of the distribution of scores on the necessity subscale, some participants objected to the view that life would be difficult without the oral chemotherapy medication and that they would become very ill if they did not adhere to their treatment. The weakest necessity belief statement was *"My life would be impossible without my medicines"* with 35.6% (n = 21) of participants disagreeing with the statement. In addition, the statement *"Without my medicines I would be very ill"* indicated that 18.7% (n = 11) of participants did not share this view.

For the BMQ-C subscale, 44.1% (n = 26) indicated strong concerns about the the oral chemotherapy treatment. However, analysing individual items on the scale revealed that worries about their understanding of their medication, lifestyle disruption, and perceived risk of dependence were particularly prevalent. The highest treatment concern was *"my medicines disrupt my life"* with 40.7% (n = 24) of patients supporting this statement. Also, 35.6% (n = 21) had strong concerns with the statement *"My medicines are a mystery to me"* and 32.2% (n = 19) agreed with the statement *"I sometimes worry about the long-term effects of my medicines"*.

4.5.2 BMQ – General Subscales (BMQ-G)

The frequencies of the BMQ-G general subscale summarised in *Table 4.6* highlights the participants beliefs about medications in general.

Table 4.6 Beliefs about Medicines General Scale (BMQ-G) with mean and standard deviation (SD) values.

	Number (%) of participants						
	Mean	SD	Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
3. BMQ – General Scale							
Doctors prescribe too many medicines	3.1	1.0	1 (1.7)	23 (39)	10 (16.9)	21 (35.6)	4 (6.8)
People who take medicines should stop their treatment for a while every now and again	2.5	1.0	8 (13.6)	26 (44.1)	12 (20.3)	13 (22)	0
Most medicines are addictive	2.6	1.0	6 (10.2)	27 (45.8)	12 (20.3)	12 (20.3)	2 (2.4)
Natural remedies are safer than medicines	2.6	0.8	1 (1.7)	29 (49.2)	22 (37.3)	6 (10.2)	1 (1.7)
Medicines do more harm than good	2.1	0.8	9 (15.3)	32 (54.2)	10 (16.9)	7 (11.9)	1 (1.7)
All medicines are poisons	2.3	0.9	9 (15.3)	32 (54.2)	10 (16.9)	7 (11.9)	1 (1.7)
Doctors place too much trust on medicines	2.5	0.8	2 (3.4)	36 (61)	13 (22)	7 (11.9)	1 (1.7)
If doctors had more time with patients, they would prescribe fewer medicines	3.3	1.0	2 (3.4)	14 (23.7)	13 (22)	26 (44.1)	4 (6.8)

According to Table 4.6, some participants held strong general beliefs about the addictiveness of medicines, the perceived harm caused by medicines outweighing their benefits, and the understanding of medicines as poisonous. Twenty-two-point seven percent (n = 14) held

strong beliefs with the statement – *“most medicines are addictive”*, and 13.6% (n = 8) in both the statements – *“medicines do more harm than good”* and *“all medicines are poisons”*.

Assessing the individual item scores also revealed that participants had general beliefs concerning the prescribing of medicines, with 42.4% (n = 25) of patients holding strong beliefs to the statement, *“Doctors prescribe too many medicines.”* In addition, over half of the participants (50.9%, n = 29) indicated that consultation times with their healthcare provider (i.e., doctor) had an impact on the number of prescribed medicines (statement – *“If doctors had more time with patients, they would prescribe fewer medicines”*).

4.6 Summary

The first unit of analysis was a questionnaire survey, which 59 participants completed. The mean age of the participants was 65.7 years, and capecitabine was prescribed as the oral chemotherapy drug to the vast majority (96.6%) compared to trifluridine and tipiracil HCl (3.4%). The MARS sum score was calculated for all participants that had completed responses to the survey. Almost two-thirds of the participants (64.4%) were classified as adherent (MARS score = 40), whereas 35.6% were non-adherent to one or more of the eight MARS statements. However, only 5.1% of study participants had MARS scores below 90%, indicating high adherence to oral chemotherapy agents. The mean and median adherence scores were 39.41 (98.5%) and 40 (100%), respectively. Forgetfulness and patients deciding to miss a dose were the most common reasons for non-adherence. Furthermore, preliminary analysis using data from the 2011 census of Welsh statistics, which identified the WIMD of relative deprivation, indicated a statistically significant ($p = 0.0002$) difference (Q1: 8/15, 53.3% vs.

Q4: 14/19, 73.7%) between the most deprived (quartile 1) compared to the least deprived (quartile 4). Further research using a larger sample would enable a more robust statistical analysis of the MARS items' capacity to differentiate between WIMD categories.

Data from the BMQ questionnaire indicated that the necessity of the oral chemotherapy medication outweighed the treatment concerns. However, participants were concerned about lifestyle interruptions (40.7%, n = 24), long-term side effects (32.2%, n = 19), and medication comprehension (35.6%, n = 19). In addition, the weakest beliefs about general medicines were regarding the addictive nature of medicines (22%, n = 14), medicines causing more harm than benefit (13.6%, n=8) and medicines being poisonous (13.6%, n = 8). The key results of the survey are summarised in *Table 4.7*.

Table 4.7 Summary of the main results from the questionnaire surveys.

	Objective	Results
Unit of Analysis 1	Assess sociodemographic status and patient adherence to medication using the Medication Adherence Report Scale (MARS).	<ul style="list-style-type: none"> • A questionnaire was completed (n=59): 55.9% (n=33) diagnosed with colon and 44.1% (n=26) with rectal cancer. • Mean age - 65.7 years (SD=10.7) and range between 42-82 years old. • Mean number of total prescribed medicines - 3.2 (SD=1.9) with 25.4% (n=15) prescribed a single medication. • 96.6% (n=57) received capecitabine (Xeloda®) and 3.4% (n=2) reported receiving Trifluridine + Tipiracil (Lonsurf®). • WIMD Data: 50.9% (n=30) lived in the two highest quartiles for most deprived compared to 49.2% (n=29) in the quartiles for least deprived. <p>Medication Adherence Report Scale (MARS)</p> <ul style="list-style-type: none"> • 64.4% (n=38) were adherent to their medication. The mean and median adherence rate were 98.5% and 100% respectively. • The adherence scores were between $\geq 95\%$ - $< 100\%$ for 30.5% (n=18) and $\leq 90\%$ for 5.1% (n=3) of patients. • 35.6% were non-adherent to one or more MARS statements. Forgetfulness (28.8%) and deciding to miss a dose (8.5%) were the most common statements for non-adherence. • WIMD Data: Patients living in the most deprived areas (quartile 1) in South Wales had the lowest adherence score at 53.3%. Patients living in the least deprived areas (quartile 4) had the highest with 73.7%. Preliminary analysis indicated a statistically significant difference between the most deprived (quartile 1) compared to the least deprived (quartile 4).
Unit of Analysis 1	Examine patients' beliefs about treatment influence (necessity and concerns) and commonly held beliefs about medication using the Beliefs about	<p>BMQ Treatment Necessity and Concerns</p> <ul style="list-style-type: none"> • The scores indicate on average, beliefs in treatment necessity outweighed concerns about the oral chemotherapy medication. 93.2% (n=55) scored over 12.5 for the BMQ-N subscale and 44.1% (n=26) for BMQ-C. • For the BMQ-N: the weakest necessity beliefs were that life would be impossible without the medication (35.6%) and of becoming very ill without them (18.7%).

	Medicines questionnaire (BMQ).	<ul style="list-style-type: none"> • For the BMQ-C: the most common concerns were disruptions to their way of life (40.7%), understanding of the medicine (35.6%) and the long-term effects (32.2%). <p>BMQ General Scale</p> <ul style="list-style-type: none"> • 55.9% held strong beliefs towards medicines in general. Some patients held strong general beliefs about the addictiveness of medicines (22.7%), medicines doing more harm than good (13.6%) and medicines being poisonous (13.6%). • 42.4% held strong beliefs that doctors prescribe too many medicines and 50.9% indicated that increased consultation times would result in fewer prescribed medicines.
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Chapter Five

Findings: Unit of Analysis 2

5.1 Introduction

The second embedded unit of analysis was an exploratory study with colorectal cancer patients, and the purpose was to assess the following objective of the research:

- Explore the challenges to oral chemotherapy medication adherence and identify factors that influence medication taking behaviour among colorectal cancer patients.
- Triangulate the evidence sources to develop a comprehensive understanding of the phenomena.

This study presents the exploratory findings from the semi-structured interviews. It provides details of the sociodemographic characteristics and sample features of the participants. The final analytical framework and the overarching themes that underpin the findings are also presented. The outcomes of this study are triangulated with results from the first embedded unit of analysis to provide a holistic understanding of adherence to oral chemotherapy medication among colorectal cancer patients.

5.2 Sample Characteristics

In general, the interview sample's sociodemographic features were comparable to those of the survey sample reported in *Table 4.1*, making it representative of the

overall cohort. *Table 5.1* presents the sociodemographic characteristics, current treatment, and cancer condition of the interviewed cohort. The mean age was 65.3 years old (SD = 10.5, range = 42-80), and the majority were married (75%, n = 12). Most of the participants were either retired (50%, n = 8) or unable to work (25%, n = 4), with only 25% (n = 4) employed. The educational level indicated that 31.3% (n = 5) held a professional diploma equivalent or above, including one participant holding a bachelor's degree; however, 25% (n = 4) had no qualifications.

The oral chemotherapy medication prescribed for the majority (93.8%, n = 15) of the interviewed cohort was Capecitabine (Xeloda®), and one person (6.2%) was prescribed Trifluridine + Tipiracil (Lonsurf®). Furthermore, 62.5% (n = 10) were diagnosed with colon cancer, and 37.5% (n = 6) were treated for rectal cancer. The mean number of total prescribed medications was 3.2 (SD = 1.9).

Table 5.1 Sociodemographic characteristics of interviewed participants.

Participant Characteristics	Participants (N)	Percent (%)
Gender:		
Male	12	75
Female	4	25
Age:		
41-50	2	12.5
51-60	3	18.8
61-70	7	43.8
71-80	4	25
Mean = 65.3 SD = 10.5 Range = 42-80		
Cancer Diagnosis:		
Colon	10	62.5
Rectal	6	37.5
Prescribed Oral Chemotherapy medication:		
Capecitabine (Xeloda®)	15	93.8
Trifluridine + Tipiracil (Lonsurf®)	1	6.2
No. of prescribed medication(s):		
1	4	25
2	3	18.8

3	2	12.5
4	1	6.3
5	3	18.8
6 or more	3	18.8
Mean = 3.2 SD = 1.9		
Ethnicity:		
White	16	100
Marital Status:		
Single	2	12.5
Married	12	75
Divorced	2	12.5
Area of Residence:		
Blaenau Gwent	1	6.3
Bridgend	3	18.8
Caerphilly	5	31.3
Newport	3	18.8
Rhondda Cynon Taff	1	6.3
Torfaen	2	12.5
Vale of Glamorgan	1	6.3
Education:		
1 or more GCSE'S	3	18.8
1 or more O Levels/A-Levels	3	18.8
Professional Diploma or equivalent	4	25
Bachelor's Degree	1	6.3
No Qualifications	4	25
Other	1	6.3
Employment Status:		
Employed	4	25
Retired	8	50
Unable to Work	4	25
Welsh Index of Multiple Deprivation (WIMD)*		
Quartile 1 - Most deprived	4	25
Quartile 2	3	18.8
Quartile 3	3	18.8
Quartile 4 – Least deprived	6	37.5

*Data was taken from the Welsh Statistics 2011 census as no data was available on the NHS Wales database.

5.3 Final Analytical Framework

The final analytical framework presented in *Table 5.2* was developed following the refining procedures outlined in section 3.5.4.2.1. Five key themes, twelve categories, and sixty-three codes emerged from the data analysis process.

Table 5.2 – The Final Analytical Framework. The table illustrates five themes and twelve categories. Beside each category are the sub-categories and codes that represent the findings in each category.

Themes	Category	Sub-Categories and Codes
Theme 1 Therapy Related Factors	Oral Chemotherapy – Dosing Regimen	Following Instructions –following recommended instructions of the medication and instructions from the healthcare provider; following instructions, trust in HP, burden and chore.
		Routine – Having a daily routine with the oral medication, its effects on adherence, and the implications of disruptions to participant routine; rigid routine, habit.
	Adverse Effects of the Treatment	Side Effects - The adverse effects of taking oral chemotherapy agents that can have an influence on medication adherence; Frustration, distress, tiredness, loss of taste, decline in quality of life.
		Impact of Adverse Effects – This denotes the extent to which adverse effects can have an impact on other factors, such as discontinuation, which leads to non- adherence; stoppage/pause in treatment, additional treatment, dose reduction, confusion.
Theme 2 Patient Related Factors	Forgetfulness	The extent to which a participant forgets to take their medication; morning dose, evening dose, breaks in routine, apprehension.
	Ownership and Responsibility	The participant’s ability to take responsibility for the outcome of their condition, self-manage their medication, and respond to and adhere to their medication; responsibilities, self-management.
		Reminder Systems - This represents the different forms of prompts that participants use as a reminder to take their medication and how this influences adherence to their medication; alarm system, family support-reminders, keeping record, eating times, pillbox.
	Knowledge and understanding	Knowledge about the oral chemotherapy medication - Denotes the level of understanding and knowledge about their oral chemotherapy medication and their condition. It also represents where the knowledge is gained, and the source of information used to gain the knowledge; source of knowledge, understanding.
		Perceived Effectiveness of the treatment - This refers to the extent to which the participant understands the purpose of the oral chemotherapy medication and its perceived effectiveness; expectation, taking it for a reason, back-up treatment, poison, alternative treatment.

	Treatment Needs and Concerns	<p>Treatment Needs - This refers to the participants overall expectations about the necessity of the oral chemotherapy treatment; determination & perseverance, tolerance, staying alive.</p> <p>Treatment Concerns - This denotes the participants concerns about the oral chemotherapy treatment that may influence adherence to the medication; long-term effects, side effects, difficulty swallowing tablets.</p>
	Effective Treatment Behaviours	<p>Attitudes – This represents how participants feel about taking the oral chemotherapy medication – both positive and negative emotions; positive attitude, confidence, negative attitude.</p>
		<p>Depression and Anxiety (Low Feelings) – This refers to the mood disorder associated with taking oral chemotherapy medicines, which causes low feelings; low feelings, hopelessness, anxiety, depression, withdrawn.</p>
		<p>Family History - The degree to which a participant experience of the chemotherapy treatment procedure either personally or through other people has influenced their adherence to the medication; family history, hopelessness,</p>
<p>Theme 3 Condition Related Factors</p>	Co-morbidities	<p>This represents other health conditions that a participant may have that can affect their adherence to their medication; drug interactions, pre-existing conditions.</p>
<p>Theme 4 Healthcare System Related Factors</p>	Knowledge and Skills Transfer	<p>Knowledge and Skills Transfer - This indicates the participants preference for knowledge and information transfer about their treatment; patient engagement, patient preference, decision making.</p>
		<p>Confidence in Doctor’s and the function of the Multidisciplinary Care team (MCT) - This represents the participants perception of the doctor’s and wider healthcare teams’ roles in their care and how it may influence medication-taking behaviour; trust in doctors, multidisciplinary team.</p>
	Development of Healthcare Services	<p>The extent to which participants have access to healthcare providers and services. The capacity of the system to educate patients and provide follow up services. Also, the impact of clinical waiting times on adherence behaviours and disclosure of information to healthcare providers; accessibility to HP, waiting times.</p>

Theme 5	Support Network and Social Impact	Family/Friends Support - Denotes the extent of a participants support system throughout the treatment regime and its influence on medication adherence; family support, living alone.
		Lifestyle Changes – The extent of the changes to participants lifestyle due to taking oral chemotherapy agents influences their adherence decisions; change of lifestyle, withdrawn.
	Social and Economic Related Factors	Economic Impact

5.4 Theme 1: Therapy-related Factors

The therapy-related factors theme consisted of the following categories:

- **Oral Chemotherapy dosing regimen** – this category consisted of two subcategories: following instructions and having consistent daily routine. Codes: following instructions (FI), trust in HP (THP), burden, chore (C), rigid routine (R), and habit (H).
- **Adverse Effects of the treatment** – this category consisted of two subcategories: side effect and impact of adverse effects. Codes: Frustration (F), distress (D), tiredness (T), loss of taste (LT), decline in quality of life (QOF), breaking point (BP), stoppage/pause in treatment (S), additional treatment (AT), dose reduction (DR), confusion (C).

5.4.1 Oral Chemotherapy Dosing Regimen

5.4.1.1 Following Instructions:

Following instructions highlighted the participants' interpretation of adhering to the drug dosing regimen and the challenges associated with taking the tablets twice a day. Participants generally believed they took their medication as prescribed, were accustomed to following instructions, and would adhere strictly to them.

"I do adhere to it as much as I can, really. I do always follow like instructions that always say they have to be a certain time of the day, after food. I have always been religious timewise"
(P000016, FI, pg.5).

The MARS survey results reflected these viewpoints, with 64.4% of respondents achieving a MARS score of 40 (100%). Participants who were adherent followed dosage instructions

consistently and viewed clinicians' recommendations as an important determinant in medication adherence.

"I'm no expert on these matters; they are the experts, and if they tell me I need to take a course of chemotherapy, I would be a fool not to go along with it...I've got no problems taking medication." (P000006, THP, pg.7).

Several participants believed that adhering to their oral chemotherapy medication was the right thing to do and that by placing their trust in their healthcare providers to look out for their best interests, their health would improve. The BMQ-N treatment necessity survey reflected this perspective positively, with 81.3% (n=48) holding strong treatment beliefs with the statement, *"My health in the future will depend on my medicine."*

There were differences in how participants approached the dosing regimen, with some strictly adhering to the 12-hour tablet interval as instructed on the drug label, whereas others were able to take the medication within the 9–12-hour time range after receiving advice from their healthcare clinicians about the time of the dose. Three individuals, however, considered the dosing regimen as a 'chore' or 'burden', due to the influence everyday medication had on their way of life.

"It feels like a bit of a...a bit of a chore every day, twice a day. I don't know why because it's only a matter of popping pills in your mouth. But you always have to remember." (P000034, C, pg.4)

Participants considered the challenges of the dosage interval as restrictive to their way of life in a variety of ways, including remembering to take the medication twice a day. These issues revolved around eating and sleeping habits, as they were concerned about taking the tablets

on an empty stomach. It was felt that the evening dose would require them to eat late at night, necessitating an earlier breakfast time to ensure that the evening dose was taken at a reasonable time.

In one case, the participant made the decision not to take his medication on the day he was scheduled to receive intravenous (IV) oxaliplatin treatment at the clinic. This decision-making was consistent with the 8.5% of respondents that were not adherent to the MARS statement, *"I decide to miss a dose."*

"I came to a decision not to take it on the same day... I also realised I didn't want to mix it on the same day anyways...I haven't told anybody other than you, but I'm pretty sure one of the nurses advised me anyways not to take it on the day."(P000055, FI, pg.3-4)

This suggests that a small sub-group of participants may decide to make their own decisions with regards to adherence decisions. The participant felt that combining the two forms of chemotherapy treatment would reduce the effectiveness of the combination IV chemotherapy if taken alongside the oral chemotherapy medication as prescribed. Further inquiry also revealed that the participant had not discussed the matter with his healthcare provider prior to making the decision to reduce his intake.

5.4.1.2 Routine

Participants considered that having a consistent daily routine gave them a predictable day and helped them remember to take their tablets correctly.

"You know you've got to take these things, so you get into a routine then." (P000006, R, pg.4)

Some participants argued that having a routine was necessary, citing the importance of the medication as a reason for developing a daily routine that helped them adhere to their treatment. It was also evident in the BMQ-N subscale, with 93.2% (n=55) firmly believing that the oral chemotherapy medication was necessary.

"...as I've gone on, it's just routine now...Now I just fire them down with a pint of water and just get on with it." (P000056, H, pg.8)

In the same way, as the participants became more familiar with their treatment, the novelty of taking the oral medication lessened. This was partly because the dosing schedule had become a regular part of their daily routine.

5.4.2 Adverse Effects of the Treatment

5.4.2.1 Side Effects

The experience of one or more treatment-associated side effects was reported by 87.5% (n=14) of the interviewed cohort. The most frequently reported side effect was hand-foot syndrome (HFS), which nearly two-thirds of the interviewed participants reported. Pins and needles, which were painful and left them with numb hands and feet, were considered distressing and made it difficult for them to walk and grasp objects. In addition, The BMG-G general scale indicated that 13.6% (n=8) held strong beliefs in the statement, *"medicines do more harm than good"*.

"...you're not doing what you want to do. I enjoy doing my gardening, I mean, it's not gardening weather at the minute, but there are still things you can do. But I can't go out there

and touch cold plants...it was still giving me that tingling in the arms...I can't do the things...it's like frustration." (P000047, F, pg.3-4).

Participants shared the sentiment that the cold sensitivity in their hands prevented them from performing routine tasks in several cases, such as gardening, based on their experiences with HFS. This appeared to be one of the main sources of frustration with the side effect profile, as participants felt that taking the medicine restricted their ability to live a normal life.

The feelings of distress were expressed by four participants who experienced symptoms of diarrhoea after taking the oral chemotherapy drug, with two individuals having severe bouts of diarrhoea. After calling the clinical helpline, one of the participants' treatments were interrupted for a period of time, and he was instructed to stop taking his tablets until the bout of diarrhoea had passed.

"...what was coming out of me was frightening me. It was like I'd say, it was glycerol; it was clear." (P000021, D, pg.9)

The participant felt as though he was leaking glycerol-like fluid, which was concerning because he had never previously encountered such symptoms. Following a medical assessment with their healthcare professional, a dose reduction was implemented in both cases, resulting in symptom relief.

In addition, one participant expressed concern after developing sores around the mouth and gums, which had progressed to small ulcers. The participant described how the symptoms appeared unexpectedly, which he described as a dramatic experience.

"I did have mouth ulcers bad, very dramatic they came on very quickly. One minute I was alright, one day I was alright, the next day I had a mouth full of pus – 12-15 ulcers which shocked me a bit."(P000019, D, pg.3)

The intense experience caused them to wonder whether continuing with the treatment was the right thing to do. The participant took the initiative to talk to the nurse about the issue and was subsequently prescribed a suitable mouthwash that helped clear up the ulcers.

The persistent tiredness or exhaustion indicated by more than half of the interviewed cohort (56.3%, n = 9) had an effect on the participants' feelings towards the treatment and contributed to the decline in their social activities. Several participants felt they were not used to feeling constantly exhausted and that, in some instances, the tiredness caused them to fall asleep during the day in some circumstances.

"I am more tired; I'm nodding off, which I never used to nod off in the evening"(P000054, T, pg.2).

It was felt that the tiredness did not appear to improve with rest, resulting in a considerable reduction in their quality of life that reached a breaking point.

"You get to a point where the side effects and the tiredness...you get to that point you think, 'I've had enough of taking this now'." (P000047, BP, pg.5)

After three cycles of treatment, this participant was still feeling fatigued, which was negatively affecting his attitude towards the oral chemotherapy medication. The participant described how the tiredness had left him at a breaking point with the medication as it was taking away his independence.

Two participants reported experiencing bouts of vomiting with the oral chemotherapy medication during the first week of each treatment cycle. Episodes of vomiting impaired the participants' quality of life and appetite, as they were unable to tolerate any foods or liquids during the first cycle week of taking the medicine. Both individuals were receiving a combination of capecitabine and oxaliplatin (XELOX) and were previously informed that they may encounter chemotherapy-induced nausea and vomiting as a possible side effect of the treatment. Antiemetic tablets with Dexamethasone were provided, as confirmed by the individuals, as a precautionary measure to prevent nausea and vomiting.

"The only tablet that I don't take is the Dexamethasone, which you've got to take for three days. I've reduced them to only taking them the once with breakfast because, after the first lot I had, I was finding it was keeping me awake all night with hiccups."(P000047, QOF, pg.4-5)

After the first cycle of treatment, one participant decided not to adhere to the dosing regimen by reducing the dexamethasone dose because hiccups were keeping him up at night and affecting his quality of life. However, the issue was raised with the nurse at his next appointment, and he was prescribed indigestion tablets for the hiccups, which he used occasionally.

A quarter of the interviewed cohort (n=4) reported a loss or alteration in their sense of taste since starting the oral chemotherapy treatment. Participants considered it important to take their oral chemotherapy medication with meals, as this was what the drug label recommended.

"...half the taste is gone, so I'm not enjoying my food as before I started the chemotherapy." (P000054, LT, pg.10)

Participants described how they were left with a film-like coating in their mouths, resulting in a tasteless palate. It altered their taste buds while eating, and some individuals described it as a mouthful of wax. A change or loss of taste had an effect on the participants' daily lives, influencing their negative attitudes regarding the treatment, their appetites and their overall eating habits.

These findings suggested that individuals perceived side effects to be distressing and restrictive to their lifestyle, which impacted their attitudes and behaviours towards the oral chemotherapy treatment. This could be a direct result of oral chemotherapy treatment, or it could be heightened when combined with other medications. Nonetheless, it must be considered that participant experiences may be influenced by several factors, such as participants receiving different oral chemotherapy agents' (e.g., capecitabine or trifluridine and tipiracil HCl) at different stages of their illness journey; as a result, their experiences and, consequently, their adherence behaviours are likely to be affected. In the section that follows, the impact of side effects across the course of therapy is discussed, and the extent to which they may influence medication non-adherence is examined.

5.4.2.2 Impact of Adverse Effects

One-fourth (n=4) of the interviewed cohort discontinued or paused their oral chemotherapy treatment in response to adverse effects. These individuals were advised not to restart treatment until their symptoms had improved or they were examined by a healthcare professional at their next cyclic appointment.

"There was a couple of the times in the 2nd session where I wasn't very well and I rang up and they told me to stop taking the tablets...the 3rd session was the only one where I started from the beginning and I completed the tablets without stopping."(P000051, S, pg.4)

Two cases of infections were responsible for half of the stoppages, and severe bouts of diarrhoea occurred in another case. In addition, one participant's oral chemotherapy medication was discontinued based on blood test results rather than clinical symptoms, although the individual expected to resume treatment at a later date. Participants were apprehensive about their susceptibility to adverse effects and infections as a result of their discontinuation experiences. For instance, infections were believed to be recurrent and left participants feeling weary, with considerable fatigue and joint pains.

"I was treated for sepsis in between my treatment...I kept on getting infections even though they said the chemotherapy would affect that and stop the healing and could make the infections...they used to make me feel dreadful absolutely awful."(P000034, S, pg.8).

A minority of participants (n=3) reported episodes of infection, which in one case resulted in treatment for sepsis. In all cases, the individuals decided to contact the clinical helpline and were immediately referred for examination and treatment. Participants were generally concerned about contracting an infection and the possibility of sepsis resulting from an illness. Participants felt they were aware that, when having oral chemotherapy treatment, their immune systems could render them more susceptible to infections than usual and that, if left untreated, deterioration could occur quickly and sometimes without an obvious sign of an illness.

Several of the participants' adverse reactions necessitated additional medical intervention. In order to help relieve symptoms, additional treatments were prescribed to 43.8% (n=7) of the

participants, and these unpleasant experiences left some individuals with negative attitudes towards their treatment.

"The side effects with it, they give you tablets to counteract it, they give you different medications for what it is...I took so many tablets I couldn't tell you." (P000004, C, pg.1)

Some individuals who had experienced episodes of diarrhoea and vomiting were provided tablets when these symptoms arose. Furthermore, one individual was prescribed further treatment after developing a blood clot that had spread to other organs, and in this case, the clot was detected early.

"From now on I'm on long term blood thinning tablets. I mean giving myself an injection every day for 6 months was an absolute nightmare." (P000016, AT, pg.12).

"I do think myself sometimes do I really need to be taking this medication? It could be gone and I'm putting myself through this and I don't need to." (P000016, F, pg.17)

The participant described her situation as a nightmare because she was required to have daily injections for six months and was subsequently prescribed long-term blood thinning medication as a prophylaxis. Consequently, some participants were concerned about adherence to the oral chemotherapy medicine because of the harm and frustration caused by side effects and subsequent complications, and hence expressed doubts about continuing to take the tablets.

Some participants disclosed that the additional medication caused them to become confused and lose track of their tablets. Likewise, the survey results from the BMQ-G General scale revealed that 42.4% (n=25) of respondents strongly agreed with the statement – *"Doctors prescribe too many medicines"*. Repeated adjustments in treatment regimens to counteract

the side effects were thought to be the cause of the confusion. One individual intended to consult the pharmacist for medical advice because of the number of changes in his treatment.

"I'm going to see my pharmacist and doctor to try and sort out these tablets basically. Because I kept changing them you know, it was getting a bit mixed up really." (P000051, C, pg.7)

This highlighted concerns regarding the inability of participants to accurately identify their tablets, since it may increase the possibility of inadvertently taking the wrong medication, resulting in non-adherence and potentially more severe outcomes.

An adjustment in the dose of the oral chemotherapy medicine appeared to improve the patient's tolerance to the medication.

"The problem I had when I was ill with the diarrhoea was, I was on too strong a dose. They've subsequently dropped the dose by 20% and I'm coping with it a lot better now. I don't get the diarrhoea." (P000021, DR, pg.8).

As a result of the side effects, 43.8% (n=7) of the interviewed cohort had their oral chemotherapy medicine dose reduced. Several patients stated that once the dose was reduced, they were able to tolerate the medicine better, which improved their attitude towards the treatment.

5.5 Theme 2: Patient-related Factors

The patient-related factors theme consisted of the following categories:

- **Forgetfulness** – the extent to which a participant forgets to take their oral chemotherapy medication. Codes: morning dose (M), evening dose (E), breaks in routine (BR), apprehension (A).

- **Taking ownership & responsibility** - The participant's ability to take responsibility for the outcome of their condition, self-manage their medication, and respond to and adhere to their medication. This category also consisted of one subcategory: reminder systems. Codes: responsibilities (R), self-management (SM), alarm system (AS), family support-reminders (FS), keeping record (KR), eating times (ET) pillbox (P).
- **Knowledge and perceived effectiveness of the oral chemotherapy medication** – this category consists of two subcategories: knowledge about the oral chemotherapy medication and perceived effectiveness of the treatment. Codes: source of knowledge (SK), understanding (U), expectation (E), taking it for a reason (TR), back-up treatment (BT), poison (P), alternative treatment (AT).
- **Treatment Needs and Concerns** – this category consists of two subcategories: treatment needs and concerns about the treatment. Codes: determination and perseverance (DP), tolerance (T), staying alive (SA), long-term effects (LSE), side effects (SE), difficulty swallowing tablets (DS).
- **Effective Treatment Behaviours**- this category consists of three subcategories: attitudes, depression and anxiety (low feelings), and family history. Codes: positive attitude (PA), confidence (C), negative attitude (NA), low feelings (LF), hopelessness (H), anxiety (A), depression (D), withdrawn (W), family history (FH).

5.5.1 Forgetfulness

Non-adherence to the oral chemotherapy medicine was related to forgetfulness. Of the interviewed cohort, 62.5% (n=10) stated that they had forgotten to take at least one dose during their treatment, and the MARS survey revealed that 28.8% were not fully adherent to

the statement, *"I forget to take it."* However, only five out of ten (50%) individuals who reported forgetting a dose in the interviews also indicated forgetting a dose in the MARS survey, implying the possibility of recollection bias and social desirability.

Participants found it difficult to find the time to take their oral chemotherapy medication twice daily when their daily routine was disrupted because it required a great deal of discipline.

"Some situations is if I change my routine. If I set my alarm for 8.15 am, I get up, and I have my breakfast I have my tablets. But sometimes, if I have an early appointment somewhere, I have to go out for 10.00 am I get up in a bit of a rush..." (P000016, BR, pg.6)

Participants described a break in routine, such as socialising with family or friends, as being a key influencer of adherence. This was reflected in the BMQ-C concerns scale, with 40.7% (n=24) of respondents expressing strong treatment concerns in response to the statement, *"my medicines disrupt my life."*

Some patients reported that the evening dose was the most likely of the two to be forgotten due to exhaustion. This was believed to be primarily due to tiredness, which was one of the most frequently reported side effects of the oral medication among the interviewed cohort.

"It's always the evening ones as most likely get up for breakfast and you know your tablets are coming after it...in the night when you're a bit tired and you been out or something, that's when I have forgotten."(P000054, E, pg.6)

The morning dose also contributed to some patients forgetting their medication.

"They're the only tablets I take in the morning so it's normally the morning one I forget if I do forget anything. It's usually around once a fortnight I would forget." (P000055, M, pg.5)

It was felt that an early morning task, such as commuting to work or attending a clinic appointment, would disturb their regular routines because of the disorientation in the mornings.

Moreover, some participants felt strongly about missing a dose, for example, feeling paranoid and apprehensive, and as a result, they would double-check their medication to determine if they had taken their dose due to the anxiety caused by missing a previous dose.

"It absolutely made me paranoid I was terrible...I was absolutely frantic, and it did make me paranoid for quite a few weeks. I kept going up and saying, "have I taking them?" back and forth. I kept thinking have I took my tablets?" (P000054, A, pg.7).

It raised the importance of adhering to the oral chemotherapy medication after missing a dose, as indicated by the BMQ-N necessity scale, with 72.8% holding strong beliefs to the statement, *"My health, at present, depends on my medicines"*.

"You live in more fear of actually forgetting the tablets you know... It's not going to make a big difference, which is silly because if you did forget one or sort of one odd dose, in the grand scheme of things in the matter of 6 months it's not going to make any difference. You can just tag it on to the end." (P000034, A, pg.6).

Nonetheless, a few individuals who felt strongly about missing a dose owing to the apprehension they felt afterwards made sense of the situation by explaining how missing a dose(s) would not make a substantial difference if added to the end of the treatment course. This highlighted that, while individuals were concerned about missing a dose, there was a difference in approach that can lead to over-adherence among participants who opt to add doses after their cycle term to make up for previously missed doses.

5.5.2 Ownership and Responsibility

Taking ownership and responsibility was considered a strong characteristic in terms of its impact on medication adherence. Some participants felt strongly about adherence to the oral chemotherapy medication, believing it was not only their personal responsibility, but also a responsibility to their loved ones.

"...to me it's an individual responsibility and duty to oneself and one's family to adhere to this medication." (P000021, R, pg.19)

The BMQ-G general scale supported the view of adherence to the medicine, with 57.7% (n=34) disagreeing with the statement – *"people who take medicines should stop their treatment for a while every now and again"*. Some individuals described the impact of the diagnosis and subsequent chemotherapy treatment on their families, and as a result, it was their responsibility to ensure they followed the treatment recommendations. One participant, for example, was in charge of caring for his wife, who had suffered a stroke while undergoing chemotherapy treatment.

"...the problem we've got at home is that because it's not just me that's not very well it's wife who's similar but with a stroke."(P000051, R, pg.2)

The participant felt responsible for making sure that his wife was adequately cared for despite his own health concerns. To achieve this, he was committed to taking his oral chemotherapy medication so that his own health could improve, as well as to requesting assistance from the larger care support team.

Furthermore, some participants felt more adept at managing symptoms after a few encounters with certain side effects, which was a feature of taking ownership of their medication.

"...after a little while I realised, I could manage it myself...when they come on by taking the anti-diarrhoea tablets myself, I realised I could manage it myself." (P000012, SM, pg.9)

"I do get very tired especially the first few days I take the capecitabine...again I've learnt how to manage that, and I know when I can do something and when I can't"(P000016, SM, pg.4)

It was felt they could self-manage the symptoms such as diarrhoea and tiredness because they were familiar with them from personal experience or dealing with family or friends going through a similar experience. For instance, one individual knew what to expect and how to self-manage diarrhoea symptoms due to years of exposure to cancer in his family. The ability to self-manage symptoms suggested that individuals may endure certain adverse effects of the medication, allowing them to continue treatment.

5.5.2.1 Reminder Systems

Several participants used practical methods to help them with self-managing their oral chemotherapy medications. Reminder methods were used to prompt or aid the memory of patients to ensure they adhered to their medication. Three individuals found it useful to prepare their medication in pill boxes as a way to remind themselves about their doses throughout the day.

"I got a box in my kitchen which I put the tablets in for the day, morning, afternoon and at night. I have a look at that and if I see them, I've got to take them...it's a pill box they call it I think...It is useful, very useful." (P000004, P, pg.5)

It was considered useful to prepare their medication boxes on a weekly basis or to prepare the medication the night before in readiness for the next day.

Setting mobile alarms was considered useful for morning and evening doses to remind themselves to take their oral chemotherapy medication.

"I take the capecitabine at 9 o'clock and I usually take the others at 10 o'clock...mobile phones are brilliant because I've got an alarm on there for 8 o'clock, 9 o'clock, 4 o'clock, 8 o'clock..." (P000016, AS, pg.13).

Some participants felt that setting multiple alarms throughout the day was a helpful tool in aiding them in distinguishing between different dosing periods when being treated for other health conditions. In addition, two individuals kept a daily record of their tablets as a way of managing their worries. This was especially helpful when they had previously missed a dose(s) or were confused about whether they had taken their dose.

"...my alarm goes off and I'm writing down. I'm a lot more relaxed now than I was in the beginning with the tablets. I'm taking them a lot more relaxed now" (P000054, KR, pg.17)

It was felt that having this record available for verification at any moment made them feel more at ease. One individual also used the data to keep track of the number of days remaining in the treatment cycle.

Also, family support was thought to be an important practical factor that helped individuals with adhering to the treatment.

"My partner she would be prompt me as well like she was fantastic. She was there supporting me, and she was reminding me when it used to get nearer the time "you got take your tablets in half hour remember" and when we wanted to do something, she be like let's wait till you take your tablets then we'll do something." (P000012, FS, pg.5)

Support from family members who were actively involved in the participant's treatment regime was beneficial in circumstances where the individual had forgotten to take their medication. This assistance was also a form of verification, as it alleviated their concerns when they couldn't recall if they had taken their medication or not.

A few participants used an alternative method of reminding themselves to take their oral chemotherapy medicine by timing the consumption of tablets with their mealtimes.

"I used to coincide it say in the morning when I was having my cuppa so that was sort of a reminder. Then in the evening, when I had something to eat or drink, you know, that was sort of a reminder to me." (P000006, ET, pg.4)

Having a reminder system could be attributed in part to their understanding of the importance of taking the medication with food, as well as practical measures to help them do so. However, the ability of individuals to take their medication could be hindered if they did not have an appetite. Nevertheless, the use of practical methods for taking oral chemotherapy medicines suggested it had several uses, primarily as a tool to help with medication adherence but also to ensure that individuals had not missed a dosage by checking the pillbox or with family members.

5.5.3 Knowledge and Understanding

5.5.3.1 Knowledge about the oral chemotherapy medication

Participants who had a good understanding of the usefulness and benefits of their oral chemotherapy medication were more likely to view their treatment as a need. According to the BMQ-N treatment necessity scale, 84.7% (n=50) of respondents strongly agreed with the

statement, *“my medicine protects me from becoming worse.”* Participants were aware that they were undergoing treatment for their CRC illness, although their recall of the diagnosis and the need for oral chemotherapy medication varied.

“I cannot remember what tablets they were at the moment...I was given the medication, and I just got on with it” (P000006, U, pg. 1-2).

Five participants found it difficult to recall the purpose of the tablets or whether they were taking them for beneficial reasons. The lack of understanding was reflected in the BMQ-N necessity survey, where 42.4% (n=25) were unsure about the treatment need statement – *“without my medicine I would be very ill”*.

Several participants felt that taking the tablets was important for the prevention and spread of the disease, although it would not completely cure them.

“It can help you. It won’t cure you; it can’t cure you, but it will delay the response, slow it down” (P000004, U, pg.8).

“...it’s a fine balance between how much you can take and how much damage it does” (P000019, U, pg.15).

They did, however, believe that there needed to be a delicate balance struck between the dose of medication given to the patient and the harm caused to their bodies.

Among some of the participants, a narrative emerged in which the oral chemotherapy medication was described as *‘poison’*. The medication was referred to as a poison by 25% (n=4) of the interviewed cohort, and the BMQ-G general scale survey revealed that 13.6% (n=8) held strong beliefs with the statement – *“all medicines are poisons”*.

"You know if the poison is going into you, and you have side-effects, it's the poison that is causing them. Capecitabine is a poison after all...if you get that feeling, I think it's working otherwise your body would just reject it." (P000021, P, pg.6).

The participants considered the '*poison*' to blame for their symptoms, and the fact that they could feel the adverse effects proved the treatment was effective. Two individuals stressed the need to persevere with the dosing regimen because the treatment was fighting all cells in the body, including cancer cells that were proliferating, although they felt there was a limit to how much '*poison*' they could tolerate before reaching their breaking point. In addition, one individual described taking the tablets as consuming a modified form of '*bleach*'.

"...basically, describe it as bleach that's been adapted you know! But then if it is curing me then I'll take the bleach" (P000056, P, pg. 8-9)

The participant described himself as being wary of medicines in general, especially in the early stages of treatment, due to his '*old-fashioned*' upbringing, but he decided to take the tablets if they would help him with his condition. This suggested that, while participants perceived risks with taking the medicine (e.g., medication being a poison, bleach), the benefits outweighed these concerns. However, participants believed that there should be a balance between the severity of adverse effects that may be tolerated before treatment toxicity sets in.

According to the BMQ-C treatment concerns survey, 35.6% (n=21) of participants strongly agreed with the statement – "*my medicines are a mystery to me*". The interviews provided insights to individuals seeking further knowledge about their medicine, and the sources of information used to develop their understanding.

"...every three weeks in the clinic I'm seeing either the doctor or the pharmacist. I might ask a question or two to them..."(P000011, SK, pg.9)

Four of the interviewees revealed that they frequently wanted to learn more about their oral chemotherapy medication and would seek information from their healthcare providers during scheduled appointments, coming prepared with questions to seek clarification. In addition, several participants (37.5%, n=6) cited their family members' support as a source of information.

"The advantage here is that my wife was a sister in a hospital and used to making chemotherapy drugs. So perhaps I got more knowledge than I need."(P000019, SK, pg.11).

Two participants had family members with nursing backgrounds who would often explain their medications to them since they were well-versed in their treatment plans. Consequently, the family members took on greater responsibilities, such as explaining when the tablets should be taken and providing information about potential side effects. This, it was thought, made it easier for participants to express their concerns and ask questions about medication adherence issues.

Talking to other people who had been through similar experiences, helped some participants cope and develop a better understanding of their medication.

"I do get some sort of answers from other people...It's quite positive in some respects because they say yes, they got through it and they have been free of it for so many years now. But then of course, unfortunately you also hear of the odd person who doesn't make it through." (P000047, SK, pg.9).

Although not all of the other people's accounts were positive, the sense of shared experiences made it easier to confide in them and ask questions because they had taken the same drug or had gone through similar stages of treatment.

Almost one-third of the participants (31.25%, n=5) reported conducting their own research and utilising the internet as a source of information. Participants felt they had more free time after beginning therapy because they weren't working (or retired in some cases), therefore they spent it researching their treatment.

"I probably read into things too much...when I've seen a list of possible side effects, I thought, "oh god I don't know about this""(P000056, SK, pg.9)

In order to learn more about their treatment, participants reported spending extensive amounts of time reading online resources from various countries, which one individual referred to as a '*hypochondriac's bible*', as well as participating in chat forums where other patients shared their stories, which were often adverse experiences. For example, while conducting online research, one participant came across information that detailed several potential side effects with oral chemotherapy agents, such as the risks of increasing side effects with each treatment cycle and the likelihood of developing sepsis, which raised concerns about whether medication adherence was the right decision.

Nevertheless, two participants elected not to learn the basics of their medication for fear of increasing their anxiety.

"...unlike other people again, I didn't ask a lot of questions because I didn't want to know too much. I knew what I had, but they used to ask me if I had any questions, and I always said

'No'. Because...I don't know, I think sometimes too much knowledge is too dangerous you know (chuckles). I think I was just...ignoring it a little bit" (P000054, U, pg.9)

These participants avoided finding out about their medication and would not seek to ask healthcare clinicians questions in medical consultations. They preferred to deal with their issues privately and would prefer not to discuss their condition with friends and family members. One of the individuals, who had issues with forgetting evening doses due to tiredness, felt that learning more about her treatment constituted a risk, and the less she knew about her condition, the easier it was for her to adhere to the treatment plan. She believed that learning more about the side effect profile and speaking with others about their experiences could have a negative influence on her medication-taking behaviour, and she would prefer not to do so.

5.5.3.2 Perceived Effectiveness of the Treatment

Participants' perceptions of adherence to the oral chemotherapy medicine varied based on their treatment expectations prior to starting the oral chemotherapy medication and the likely outcomes after completing the course.

"My expectations were that they would improve my health...obviously they do it for a reason, and the reason is to bloody improve your health." (P000006, E, TR, pg.7)

Several participants considered they were taking the oral chemotherapy medication for a reason, and it was felt this confidence stemmed from the doctor's recommendations and trust in their medical knowledge (as mentioned in *section 5.4.1*). Listening to the doctors' advice was identified as an important factor in the participants' treatment, that may influence their adherence decisions. In addition, individuals who did not know what to expect from the

treatment hoped that it would eliminate the cancerous cells and believed that there was a high success rate, allowing them to maintain a positive outlook throughout. However, some individuals did not have as much confidence in the treatment.

"I believed at the time that it couldn't be operated on or treated." (P000016, E, pg.1).

"...the success of this chemotherapy is between 5 and 10%. Whether I've got it wrong or not but that is how I understand." (P000051, E, pg.3)

In the BMQ-N treatment necessity scale, 18.7% (n=11) did not hold strong beliefs with the statement – *"without my medicines, I would be very ill"*. The contrasting perspectives on the drug's success rate and usefulness highlighted that participants' perceptions of the oral chemotherapy medicine may influence their adherence decisions if they believe that their odds of survival are low. For instance, one individual diagnosed with stage 3 colon cancer believed it was only a matter of time before it became terminal, so as a result, she was thinking about how long she had to live despite her treatment options. Furthermore, 43.8% (n=7) of the interviewed cohort felt that the oral chemotherapy medication would not cure them but rather delay disease progression. Some of these individuals referred to it as a *'back-up treatment'* and *'belts-and-braces approach'* as a precautionary measure to remove any cancerous cells that remained after the surgery.

"...basically, all I know is...it's a sort of back-up treatment to make sure that nothing transpires" (P000047, BT, pg.6)

Participants who considered their medicine a secondary or 'back-up' treatment also felt that natural remedies were an alternative treatment option since natural remedies are less harmful to the body.

"I think there is probably a place for pharmaceuticals and natural medicines...I do believe there has got to be a place for them because everything is derived from something around us"
(P000047, AT, pg.12)

The BMQ-G general survey revealed that 11.9% (n=8) strongly agreed with the statement – *"Natural remedies are safer than medicines"*. One possible explanation was highlighted by a participant who was assertive about adherence to the oral chemotherapy tablets.

"I've seen it 2 or 3 times up there. And they're taking cannabis oil. And I'm going...it doesn't work...you know. They are trying everything they can to stay alive yet not realising...they hear it on the internet that it's a miracle cure...They tried it with my next-door neighbour Rachel, and she passed away two months ago." (P000021, AT, pg.22)

The participant revealed interactions with individuals undergoing similar treatment at the clinic who were taking cannabis oil, described as a *'miracle cure'*. Although he did not think it to be effective, he explained that some patients had turned to cannabis oil out of desperation. Due to their vulnerable nature, participants were more inclined to listen to accounts from other patients who had used it or read online sources as they desperately sought alternative solutions.

5.5.4 Treatment Needs and Concerns

5.5.4.1 Treatment Needs

The tolerance shown by participants in times of adversity and the determination to continue with their oral chemotherapy medication were related to medication adherence. The BMQ scores indicated that, on average, beliefs in treatment necessity outweighed the treatment concerns, with 93.2% (n=55) scoring over 12.5 for the BMQ-N subscale.

"I'm a bit philosophical about it, I would rather limp of it then be dead sort of thing. If they thought it was necessary, I would have continued and limped a bit more" (P000019, T, pg.15).

Several participants believed that adhering to the oral chemotherapy medication was necessary to their survival and were driven by this fear during treatment. This was supported in the BMQ-N treatment necessity survey, with 72.8% (n=43) of participants strongly agreeing with the statement – *"my health, at present, depends on my medicines"*.

"...I went to the hospital the following time and they said we'll give you a week's rest, but I said no let's get it over and done with...the treatment I was having it doesn't only affect one person it affects quite a lot of other people." (P000012, T, pg.9-10).

"I have a lot to live for, I've got 2 young children and I had a lovely life and I still do you know, before I was diagnosed with this, we had a good life." (P000034, SA, pg.11).

Three participants considered it important to stay alive and persevere through all adversities in the hopes of a positive outcome. This was because the treatment affected not only the individual undergoing chemotherapy but also those close to them, such as their families. Participants described experiencing side effects, yet some were reluctant to talk to their healthcare providers for fear their medication would be stopped and thus were willing to tolerate the effects. For example, one participant refused to take a week's rest from the treatment to allow his side effects to subside. The medicine dosage in each of these cases had previously been lowered in response to side effects; one of whom was treated for sepsis. However, the participants were prepared to go to great lengths to complete the therapy course in order to prevent a relapse of their illness.

Participants were motivated to adhere to the oral chemotherapy treatment because they were looking forward to returning to a normal life and watching their children and

grandchildren grow older. Consequently, individuals were required to maintain their strength of character by displaying determination and mental fortitude. One participant, for instance, recounted setting achievable goals and continuing to do so until he completed each treatment cycle.

"... I set a goal, and I can go for that goal, and once I reach it, I set another goal, and so on, you know." (P000004, DP, pg.10)

Individuals viewed their ability to display resilience as a test of character and an indication of their ability to exhibit positive personality traits.

5.5.4.2 Concerns about the medication

Several participants raised concerns about whether the oral chemotherapy treatment would work, as well as its side effects and long-term repercussions. The BMQ-C concerns subscale indicated that 44.1% (n=26) of respondents expressed strong concerns about the oral chemotherapy medication.

Some of the interviewed cohort had a desire to live a normal life and expressed concern that the medication's side effects might affect their adherence decisions.

"Am I going to feel really ill? Because, I know people say it, but even taking medication that saves your life, if it makes you feel so ill, I just couldn't really imagine that at all. I don't want to be ill. I just want to try and be as normal as possible." (P000016, SE, pg.16).

The participant's ability to endure the side effects was increased when they were aware of other individuals' negative experiences with the oral chemotherapy medication.

"That was my main concern the side effects that other people had suffered from, sickness and diarrhoea." (P000059, SE, pg.13).

One individual, for instance, purchased incontinence sheets after speaking with other patients who had received similar treatment and whose primary concern was sickness and diarrhoea. According to the BMQ-C concerns survey, 23.7% (n=14) of respondents had strong treatment concerns with the statement – *"Having to take medicine worries me."* The interviews revealed that participants were nervous about taking the drug and worried that they might have the same problems.

The BMQ-C treatment concerns survey revealed that 32.2% (n=19) of participants had strong concerns with the statement – *"I sometimes worry about the long-term effects of my medicines."* Participants were concerned about the treatment's success rate and whether they were taking the tablets for the right reasons after experiencing complications while taking the treatment (as discussed in *section 5.4.2*). Furthermore, 25% (n=4) of the interviewed cohort raised concerns about the long-term effects of the oral medication, stating that they were still experiencing symptoms weeks, or in some cases, months, after their first encounter.

"...if I stop taking the medication what is going to happen? my concern there is...what will it do to me long term? my feet are still sore, you know I got used to that basically, but I don't know what this medication is doing to the rest of me long term." (P000016, LSE, pg.17).

"That is my one worry now am I going to be left with this permanently or is it going to go away by itself?" (P000012, LSE, pg.8).

The participants were concerned about the medication's long-term implications due to the discomfort and how it might affect the rest of the body. In addition, they questioned whether

continuing with oral chemotherapy treatment could cause irreversible harm due to medication adherence and affect their quality of life in the long run.

The size of the oral chemotherapy tablets and swallowing difficulties were considered by three individuals as physical barrier to medication adherence.

"...the size of the actual tablets, with some people, they do almost look like bullets. They can be quite big, and not everybody is great at taking tablets, are they? They have to snap a paracetamol in half, and these are actually bigger than the paracetamols. These are nearly twice the size of them." (P000034, DS, pg.16).

Participants described the difficulty of taking the twice-daily tablets due to their size, with one participant comparing them to bullets. The physical properties (size and shape) of oral chemotherapy tablets relative to conventional tablets such as paracetamol were perceived as a common source of concern that could influence participants' adherence decisions. The participants reported that the product label directed them not to crush the tablets in the mouth and were apprehensive about swallowing the tablets, which tested their tolerance to the medication.

"I was worried about taking them because they were quite big and years and years ago, I choked when I was in my 20's and I was very nervous of swallowing them..." (P000054, DS, pg.10).

Due to a previous traumatic experience, one participant was anxious about swallowing tablets. She recalled a tablet becoming trapped in her throat, causing her to choke; hence, she was concerned about the size of the tablets impairing her swallow reflexes. To remedy this, the participant was given alternate, smaller tablets, which meant consuming a greater quantity of tablets to achieve the same clinical dose. This indicated that individuals have the

option to take smaller tablets; nonetheless, this would require daily adherence to a large quantity of tablets, which may present its own difficulties.

5.5.5 Effective Treatment Behaviours

5.5.5.1 Attitudes towards medication

Among the interviewed cohort, 43.8% (n=7) considered it important to develop a positive attitude toward the oral chemotherapy treatment. Participants felt that they needed to stay in high spirits throughout chemotherapy because the treatment was overwhelming at times. As a result, some participants used it as a coping mechanism to prevent the onset of self-doubt.

"I think positivity makes a massive difference! I know there's no evidence to provide, and I remember when the district nurses used to come to the house on the weekend to do my dressing, and she said, "I am really a true believer that positivity plays a massive part in how you recover." I kind of thought about things, and I thought yes...maybe that was why I had a really good response to the chemo and the radiotherapy. It was shrinking from the beginning because I was positive, and I wasn't stressed." (P000034, PA, pg.10-11)

Participants' positive attitudes suggested that they considered the oral chemotherapy medication to be essential and that optimism in their recovery would benefit them. Two individuals, for instance, channelled their emotions by refraining from worrying about the past and the future and by concentrating on the positive aspects of life.

Positive experiences with the drug at the outset were a crucial driver for individuals who developed a positive shift in attitude toward the medication. Several participants, however,

reported a lack of confidence in taking the tablets at the beginning of the treatment as they worked through the distress of being told they needed to take the oral chemotherapy medication.

"...in the beginning I said, 'I haven't got it because you've got the wrong person'. Perhaps a lot of people think like that, but I think because I felt so well...I just want to try to be as normal as possible...I think I was surprised I felt so well" (P000016, C, pg. 15-16).

"...when I started the chemotherapy, I wasn't quite sure where I was with it...the more it has gone now, like the last cycle of course, it is getting a bit better now." (P000056, C, pg.2)

The participants' initial reaction to the situation was denial, as the news was unexpected, and they were otherwise in good health. Initially, some participants also opted for a more cautious approach due to the novelty of the medication and uncertainty about the future.

"After a while, I got more confident at taking the medication, and I started going out again." (P000019, C, pg.5)

It was felt that individuals gained confidence with taking the oral chemotherapy tablets, especially those who had encountered fewer side effects and, as a result, had a more positive outlook on the treatment. One participant, for example, chose to break the mould by returning to work in a house-buying and selling business he founded. He recalled the difficult emotions he experienced in the beginning, as well as the misery of waiting to die at home. After deciding to change his mindset, he rediscovered pleasure in his hobbies, which gave him a new lease on life.

Three participants, on the other hand, had negative attitudes toward the oral chemotherapy treatment and towards medicines in general. It was felt that they would avoid taking tablets whenever possible due to their mutual dislike for them.

"If I could avoid it, I would never take tablets." (P000059, NA, pg. 10)

The negative attitudes toward the medication were attributed to the medication's side effects and the malaise caused by not knowing if the medication was working (i.e., whether the treatment was successful). Participants expressed frustration due to their inability to carry out basic chores and, as a result, their dissatisfaction with the medicine was heightened.

5.5.5.2 Depression and anxiety (low feelings)

During the treatment, 62.5% (n = 10) of the interviewed cohort had low feelings that were characteristic of depression and/or anxiety. The negative emotions varied from the initial scepticism about their condition and treatment needs, overthinking, and side effects of the tablets.

"You are very low because you don't know if they're going to work you know. Because that word beginning with 'C' frightens the life out of you...you're taking these tablets, and you are very low...you don't feel like topping yourself or anything like that, but sometimes I was thinking, 'is it worth me taking this if it's not going to work'" (P000012, LF, pg.10)

Due to their anxiety over their health, some individuals were concerned about whether the medication would work.

"It's anxiety which creates the malaise. You get worried about it." (P000021, A, pg.21)

This was supported in the BMQ-C concerns survey, which indicated that 23.7% (n=14) had strong treatment concerns with the statement – *"Having to take medicine worries me"*. Participants developed a sense of dread and negative thoughts about the value of medication adherence if their health was not going to improve.

Three participants were surprised to learn that they had to take the oral chemotherapy medication, which they believed had an impact on their wellbeing, particularly during the first two cycles of treatment.

"...it comes as a shock at the beginning...and that affected my how can I say...my whole health, my wellbeing, my outlook on life" (P000016, LF, pg.2-3)

The participants felt strong emotions during the early stages of treatment because of the overwhelming nature of the situation, which led to feelings of self-doubt and hopelessness. For example, one individual described how his depression caused him to overthink all the time, which made him even more worried.

"...mostly depression I've had. I did, in the beginning, slow down and I did sit in the house. I did think about it too much, and I was crossing dates on my calendar when I was going to die." (P000019, H, pg.17)

Participants reported having thoughts of hopelessness, especially when they were alone and had time to think about everything, which was reflective of their response to adversity through the early phases of treatment.

"I try not to let them visit because sometimes I'm a bit down...no one wants to see someone with pyjamas talking about illness." (P000021, W, pg.2)

In addition, four participants reported distancing themselves from family and friends during the chemotherapy treatment, which indicated signs of withdrawal. They preferred not to discuss their circumstances because they did not want others to feel sorry for them.

Furthermore, three participants experienced low feelings and emotions as a result of the side effects of the oral chemotherapy treatment, believing that the tiredness symptoms were wearing them down.

"When it gets you to a state where you're very weak and you can hardly walk, that is when you are at your lowest." (P000051, LF, pg. 9).

The inability to function normally due to adverse effects such as fatigue and HFS heightened the negative emotions (i.e., low feelings), suggesting that individuals may have reached a point where the risks of the oral chemotherapy medication may influence their decisions to continue taking the drug. One participant, however, decided to seek support and consult his GP about his feelings after becoming agitated about the treatment that had built up in his thoughts over time.

"I had that little man in my head for a bit for weeks " (P000058, D, pg.10).

After he sought medical advice, his GP decided to increase his anti-depressant tablets for a week, which improved his mood and overall wellbeing. The participant described how the fog over his brain had lifted after completing the course, allowing him to think more clearly and reflect more positively about the future.

5.5.5.3 Family History

A family history of cancer that resulted in mortality affected a quarter of the interviewed cohort (n=4), and as a result, they had negative emotions toward the oral chemotherapy medication.

"...my grandad had it. He had it in the colon, and my grandmother had it in the pancreas...to be honest, it killed them...I didn't want to go down the same road as my grandparents did." (P000062, FH, pg.14-15).

The participant was determined not to succumb to cancer like her grandparents had, yet she described having lingering worries. Due to their family history of cancer, participants felt a

sense of inevitability about their disease, suggesting that they considered their hereditary risks as severe and fatal, which contributed to their feelings of hopelessness and negative emotions toward the treatment. The doubts about the future and how much longer they had to live were questions that remained unanswered in their minds.

"I was a bit worried about it, and the reason for that was that my stepfather died from chemotherapy...it's still at the back of my mind now...It gives you a reason of whether to even go through the course of treatment" (P000047, FH, pg.14)

One individual felt this was one of the reasons he disliked taking medications. The participant, whose stepfather had undergone chemotherapy but unfortunately died, believed that his stepfather was given an overdose of the treatment, which his mother blamed herself for, and that was ultimately one of the reasons he disliked taking medicines. Participants expressed feelings of inevitability and reservations about taking medicines, which were heightened by the side effects of the oral chemotherapy tablets.

5.6 Theme 3: Condition related factors

The condition-related factors theme consisted of the following category:

- **Co-morbidities** - this represents other health conditions that a participant may have that can affect their adherence to their medication. Codes: drug interactions (DI), pre-existing conditions (PC).

5.6.1 Co-morbidities

Participants with pre-existing medical conditions faced complications and, in some cases, a pause in their therapy. Half of the interviewed cohort (n = 8) experienced an exacerbation or

were advised to discontinue a specific medication during the therapy period because of drug interactions with the oral chemotherapy tablets.

"I was borderline diabetic before this treatment...it almost doubled my blood sugar level and since then I've been put on Gliclazide. I've got one of these monitors that I have to take my bloods every so often. That was a bit of a shock to me it did dramatically put up my sugar levels." (P000019, PC, pg.6)

One participant, a borderline diabetic who was previously controlled with dietary foods and exercise, described his distress after his sugar levels rose while taking Capecitabine. He was later prescribed the anti-diabetic medicine Gliclazide to control his diabetes.

According to the BMQ-C treatment concerns survey, 40.7% (n=24) of respondents held strong beliefs with the statement, *"my medicines disrupt my life."* This finding was supported by the fact that certain individuals' treatment was disrupted due to contraindicated medications and/or pre-existing illnesses.

"The clinic did say that sometimes when people bowel medication, it can affect other things as well...but it's not a very nice feeling when it clouds over really" (P000054, PC, pg.14).

The perspectives of participants about treatment outcomes, such as the tolerable risk of adverse effects and in treatment benefits, varied, particularly for those who had experienced exacerbation of pre-existing conditions. It was felt that the uncertainty surrounding their illnesses (e.g., flare-ups in symptoms, drug interactions, and treatment interruptions) did not inspire confidence in their ability to take the oral chemotherapy drug.

Furthermore, individuals experiencing such complications because of pre-existing conditions may influence their medication-taking behaviour. For instance, one individual developed

uveitis in both eyes after stopping methotrexate while taking his oral chemotherapy medication. The participant had several medical issues and was having frequent epileptic fits during the first few cycles of treatment due to a drug interaction with his Phenytoin medication. In addition, he suffered from sleep apnoea, which made it difficult for him to adhere to his medicine, particularly the morning dose.

"I have severe sleep apnoea I don't know what I'm doing half the time in the mornings...sometimes I wake up quite confused" (P000055, DI, pg.6).

Following medical advice, the dose of his capecitabine was reduced, which resolved the epileptic fits, though he was still experiencing sleep apnoea, which created confusion and raised the risk of forgetfulness with the oral chemotherapy medication. This, along with other participant cases, indicated that non-adherence can occur in individuals with existing medical issues, which can be a direct cause or exacerbate adverse effects. The average age of the interviewed cohort (65.3 years old) and the likelihood of having a pre-existing ailment may be factors that lead to non-adherence to oral chemotherapy treatment.

5.7 Theme 4: Healthcare System related factors

The healthcare system-related factors theme consisted of the following categories:

- **Knowledge and Skills Transfer** - this indicates the participants' preference for receiving knowledge and engaging with healthcare providers regarding their treatment and its impact on medication adherence. This category also consists of one subcategory: confidence in doctor's and the function of the Multidisciplinary Care team (MCT). Codes: patient engagement (PE), patient preference (PP), decision making (DM), trust in doctors (TD), multidisciplinary team (MT).

- **Development of Healthcare Services** - this denotes the extent to which participants have access to healthcare providers and services and the impact of waiting times on adherence behaviours. Codes: accessibility to HP (AHP), waiting times (WT).

5.7.1 Knowledge and Skills Transfer

Knowledge and skills transfer examine the perspectives of the participants regarding their preferences for understanding their treatment and how this may influence on medication adherence. Individuals reported receiving a group educational session prior to starting the treatment, outlining specifics about the oral chemotherapy tablets, the benefits, and the potential risks associated with their use. Also, they were provided with informational leaflets containing contact details for the clinic's helpline as well as information regarding the oral chemotherapy medication.

"They tell you the basics, I think, I believe, which is enough to understand in layman's terms. Because anything else would frighten people I think." (P000021, PP, pg.11).

Participants thought that at the educational briefing they were given information about their oral chemotherapy medication that was intended for everyone to understand so as not to deter them from taking the medication. Participants referred to details regarding the nature of the treatment, the reason for taking the medicine, its side effects, and what to look out for. Nonetheless, there were a variety of perspectives on what detail individuals expected and their levels of engagement with the information provided. For example, after attending the education session, one participant found it difficult to understand the information presented due to the emotions he felt at the time and the complexity of the material.

"I don't...a lot of it when over my head" (P000019, PP, pg.11).

The participant found it difficult to absorb information about the oral chemotherapy medication due to the novelty of the situation and his initial distress. Also, some participants felt that learning about the medication's risks and side effects heightened their fears and made them less optimistic about the treatment.

"I was told on a couple of occasions about side effects and what I could get which was very off putting. They made me dread having the chemo, like they say because it's the law they have to tell you everything from what I understand." (P000059, PP, pg.8).

This suggested that participants had different preferences; therefore, providing them with standardised education sessions may not be suitable for all, as this may alter their medication-taking behaviour.

Nevertheless, even though participant preferences varied, it was evident that individuals that were engaged with their treatment wanted to learn more about their oral chemotherapy medication, which may increase the likelihood of adherence to the oral chemotherapy medication. Some participants reported that they would regularly ask healthcare clinicians questions in order to make more informed treatment decisions and manage adverse effects.

"I didn't do anything without questioning. I do what I'm told but I will question a lot...I will cross check with others, I will ask a lot of questions of everyone I come across." (P000019, PE, pg.11).

In addition, participants highlighted their openness to taking part in making decisions about their care management with their clinicians.

"I'm always open to talk about medication and changing it or whatever" (P000016, DM, pg.5)

Participants who were engaged with their clinicians about their treatment were willing to discuss any changes or side effects with their clinician in order to achieve the best possible

outcomes. However, some individuals were unsure how to approach the subject with their clinician - whether they should follow orders or to ask questions in order to reach a mutually agreed-upon treatment plan.

"But you know, is it for any patient to ask or should I be told? There's difference." (P000021, DM, pg.11).

The participant felt that he should first be provided with all treatment-related information so that he could gain a thorough understanding, and then they should engage in conversation so that they can find a mutually beneficial agreement.

However, two participants, for different reasons, chose not to engage with their healthcare clinicians about their medication and stated they avoided asking questions.

"I'm not going to ask questions when I'm running late and they're running late...I tend to step back I don't want to cause any issues. I don't want to cause more time wasting or anything else." (P000021, PE, pg.14).

The BMQ-G general survey indicated that 50.9% of respondents held strong beliefs with the statement – *"if doctors had more time with patients, they would prescribe fewer medicines."*

The participant avoided engagement due to the time limits of the consultations and therefore didn't want to bring up any issues that would cause further delays. Furthermore, these individuals were more inclined to make decisions without consulting their doctors first. For instance, one participant's decision not to take his oral chemotherapy medication had a direct impact on his adherence to the oral chemotherapy medication (as mentioned in *section 5.4.1*). The participant chose not to discuss his treatment with his doctor because he believed that too much information might be harmful and influence his attitude toward the drug. This,

however, highlighted the importance of engaging individuals in their treatment and the potential influence it may have on medication adherence.

5.7.1.1 Confidence in Doctor's and the function of the Multidisciplinary Care team (MCT)

A quarter of the interviewed cohort (n=4) believed that the MCTs, which were comprised of various healthcare clinicians such as medical doctors, pharmacists, and nurses, were experts in the area and were helping them to improve their health.

"The nurses ask you if you have been taking the medications ok and if I've had any problems with it every time I go for treatment." (P000055, MT, pg.7).

Participants expressed their satisfaction with the clinical support provided by the wider MCTs and found them helpful with resolving any difficulties with the oral chemotherapy treatment.

Nonetheless, some participants felt that their confidence in taking the oral chemotherapy medication stemmed from the doctor's recommendations and their trust in their medical knowledge.

"I've got no problems taking medication. As long as it is prescribed by a doctor, they do it for a reason and the reason is to improve your health." (P000006, TD, pg.7).

Listening to the doctors' advice was considered an important aspect of the participants' treatment, and it may influence their adherence decisions. There was a disparity in participants' preferences to be assessed by their doctor as opposed to other healthcare clinicians. Three individuals were concerned about the absence of doctors during appointments and the reasons for being assessed by the wider MCT.

"I don't know how they work that, why I see the pharmacist...I was a bit concerned about well I've only spoken to doctor once...If I haven't got any problems, she can't advise me on anything can she, you know." (P000054, TD, pg.11)

Participants assumed that there may have been reasons for the doctor's absence, such as being overworked and having low staffing levels, and that, as a result, they would only be examined by the doctor if there were issues with their treatment. This, however, did not ease their concerns because they felt the doctor played a pivotal role in their treatment. Individuals gained confidence from speaking directly with them about medication adherence issues. For example, one participant expressed his dissatisfaction with seeing the wider MCT despite the fact that they were able to provide him with the necessary medical advice.

"When you're dealing with the pharmacists, yes, she understands it all and she can probably relate it to me, right. It's like...why can't I see the boss? Why am I seeing someone further? I think then you think I'm not important enough." (P000021, TD, pg.11)

Some participants viewed their doctor as the focal point of their treatment plan, assuming an authoritative role. It also highlighted how important some participants thought their doctor's medical advice was compared to the wider MCT's, which may play a role in patient adherence to the oral chemotherapy medication.

5.7.2 Development of Healthcare Services

Over a third of participants (n=6) were dissatisfied with the amount of time they spent interacting with healthcare clinicians and their limited accessibility to talk about their issues. This created a barrier, as some participants thought time constraints made them less willing to talk about their problems.

"I know they haven't got the time, the doctors. I think they are allowed 10 minutes per patient and that's just to write up the notes...but again, that is probably down to staffing shortages, no-ones got the time to do it." (P000047, AHP, pg.12).

The lack of availability and short consultation times were attributed to the heavy workload of clinicians and staff shortages. In addition, some participants believed there was a difference in the care received before starting the chemotherapy treatment versus post-surgery care.

"I expected they would contact me as well you see. To make sure, to see how I was getting on. Initially when I was diagnosed (in Bridgend) I was getting phone calls every week." (P000011, AHP, pg.6)

Three participants felt comfortable discussing their issues with nurse specialists following surgery because they were receiving regular check-up calls, which they viewed as the most reliable source of information and support as they had established rapport with the staff. Participants did not believe it was appropriate to bring up their concerns during their appointments due to the short consultation times and busy nature of the outpatient clinic. Instead, they expected to be contacted between treatment sessions to talk about any problems they were having with oral chemotherapy treatment.

Appointment and prescription waiting times at the outpatient clinic were reasons given by three individuals for not discussing medication adherence issues. For instance, one participant expressed his frustration with the waiting times at the pharmacy to collect his medication.

"The real delay is it can be over an hour in the pharmacy. Just sitting there waiting...I sit there and wait." (P000019, WT, pg.7)

Participants expected timely access to clinicians, and delays in this and/or collecting prescriptions caused them to avoid discussing their concerns or asking questions because it would cause further delays at the clinic. For instance, one individual with several adherence-related challenges, such as forgetfulness and frequent tiredness, refrained from disclosing these issues to healthcare clinicians.

"I just tell them everything is going ok simply because I can't be bothered that means more delays at the hospital...I don't want to be waiting around to speak to doctors...there might be an hour wait and then you've got to wait longer for the ambulance to take you home"
(P000055, WT, pg.7)

Participants felt that by the time they were called by clinicians to discuss their medication, they were eager to return home and did not wish to raise concerns for fear of further delaying the process. Consequently, this indicated that waiting times have the potential to influence medication adherence behaviour, as participants were reluctant to disclose their concerns.

5.8 Theme 5: Social and Economic related factors

The social and economic-related factors theme consisted of the following categories:

- **Support Network and Social Impact** – this category consists of two subcategories: support network and lifestyle changes. Codes: family support (FS), living alone (LA), withdrawn (W), change of lifestyle (CL).
- **Economic Impact** - the extent to which the oral chemotherapy treatment impacts participants' economic livelihood and resolve during the treatment period. Codes: financial difficulty (FD), increased costs (IC).

5.8.1 Support Network and Social Impact

5.8.1.1 Support Network

Participants who had family support during their treatment spoke about the important role their families played with medication adherence. Of the interviewed cohort, 81.3% (n=13) lived with family members, and numerous participants said their spouses or children would regularly remind them to take their medication and make sure they had their supplies when they left the house.

"He does always make sure that I've got my medication and my supplies when I go out of the house because I have been caught out a few times" (P000016, FS, pg.5)

This also served to reduce the number of times participants forgot to take their medication by actively reminding them of their upcoming doses. In addition, family support catered for their emotional and physical needs, particularly when they were feeling low and during difficult periods with the medication's side effects.

Nevertheless, three participants lived alone, and according to the MARS survey, none of them adhered to all of the statements regarding their oral chemotherapy medication. All three participants were not adherent to the statement – *"I forget to take it"*, and two participants were not adherent to the statement – *"I decide to miss out a dose"*.

"I just talk to them when I want to talk to them." (P000055, LA, pg.2).

Family and friends support played a different role since they preferred to approach their family about their requirements as they were more comfortable making their own decisions. Individuals called upon their support network when they were needed. For example, when they were feeling unwell, they would contact their family to help them with their shopping,

or when they felt they wanted to talk to someone. This suggested that participants who live alone may be prone to forgetfulness and to making their own medication adherence decisions.

5.8.1.2 Lifestyle Changes

Since starting the oral chemotherapy medication, 56.3% (n=9) of the participants stated that the treatment had negatively impacted their social life, and for various reasons. Tiredness due to the medication, the fear of catching an infection, and depression were reasons given by patients for choosing to stay at home.

"It affects your social life because you're so tired...I don't go far now I just go where I got to go...it did affect my social life. I don't go out and I don't socialise like I used to, nothing like that." (P00004, CL, pg.2)

Tiredness or fatigue was one of the main side effects reported by the interviewed cohort (see section 5.4.2). It negatively affected the social activities of 31.3% (n=5) participants as the feeling of constant tiredness stopped them from enjoying their hobbies, such as gardening, socialising, etc., and left them frustrated.

"I stopped going out altogether. I was afraid in the beginning of getting an infection...missing treatment or whatever so I did virtually stop going out altogether" (P000019, CL, pg.5).

Three participants said the fear of catching an infection or cold forced them to take shelter at home, which contributed to the decline in their social activities.

Some of the participants revealed they had heard stories from other people about the risks of catching an infection and were afraid it might worsen their condition. For instance, one participant described changing his shopping routine and carrying out errands in the early

mornings in order to avoid large crowds. Furthermore, two participants decided not to socialise because they were feeling low and withdrawn due to the changes in their condition, which affected their lifestyle.

"I don't go out now. I used to a lot but since I've been diagnosed with this I don't bother going out. I keep myself to myself" (P000062, W, pg.4)

The change in habits may have an influence on his medication-taking behaviours because of his negative outlook on life. Prior to starting the oral chemotherapy medication, the participant had a busy work life, working long hours and being constantly active. However, after going on sick leave, he started to develop low feelings due to the sudden change in lifestyle and became more withdrawn.

Furthermore, two participants stated they had stopped drinking alcohol since starting the treatment after experiencing adverse effects with its consumption and, as a result, made a change in their lifestyle accordingly.

"Will advise people not to go drinking whilst you're on the medication because it doesn't mix. I went out once I've done it once and I was just vomiting all night after it...that's why I don't bother now" (P00004, CL, pg.8)

The participants used to enjoy social drinks with evening meals and during social outings, but had since decided to avoid drinking while taking the medication. The individuals no longer saw the value in continuing with this while taking the oral chemotherapy medication after receiving medical advice about its adverse effects with the treatment.

One participant, however, reported that the oral chemotherapy treatment had a positive impact on her social activities. Regular outings to scheduled appointments at the outpatient

clinic had reunited her with an old childhood friend, and she also built friendships with some of the healthcare clinicians.

"Sometimes I quite look forward to it as my little outing on a Monday morning. I mean they're obviously medical staff and whatever but there's a W.I. lady I've made friends with and, there's actually somebody I've bumped into a friend that I haven't seen bear in mind I am 62 I haven't seen her since I was about 15!" (P000016, CL, pg.4)

The participant spoke positively about her experiences, she was able to use her time at the clinic efficiently after meeting one of her childhood friends who was coincidentally on the same 3-week appointment schedule. The participant also developed strong relationships with the healthcare clinicians and was able to discuss personal matters, which she thought strengthened her resolve because she felt comfortable discussing any medication adherence related concerns.

5.8.2 Economic Impact

Nearly a third (n=5) of the interviewed cohort revealed they had incurred some loss in income since starting the oral chemotherapy treatment. Participants experienced financial difficulties as a result of being off work, taking early retirement, and travel costs to and from clinic appointments.

"It has hit me in the pocket quite hard to be honest...I'm probably losing around £1000 a month...I don't see me going beyond that 6 months because if I did it would be even harder then." (P000056, FD, pg.3)

Two participants described their financial hardship since starting the oral chemotherapy treatment, reporting that they had to take time off work in order to recover. This, however,

came at a cost, as it considerably impacted their household's monthly income. One individual, for example, expressed his frustration at losing half of his income because he was used to working overtime hours, but since taking sick leave, this revenue stream was no longer viable. The individuals reported that they did not wish to extend the 6-month cycle treatment because it would further impact their finances. This indicated that some participants faced financial hardship during the treatment, and that the longer the treatment period lasted, the greater the likelihood that individuals may be compelled to make challenging decisions regarding oral chemotherapy treatment adherence.

Furthermore, three participants were retired and dependent on state benefits, but they reported incurring extra costs since starting the oral chemotherapy medication.

"I find an issue is obviously I had to pack in my job because of the cancer ...took retirement if you like, to combat this cancer. The only income I have is my national insurance...I've lost that income for two years. As I said I went straight on the state pension." (P000021, IC, pg.2-3)

This highlighted the fact that participants with economic insecurity experienced challenges that, if unresolved, may raise their risk of nonadherence to the medication. For example, the participant had taken early retirement but was aggrieved at losing two years of income and incurring higher expenses since starting the treatment. This was because he spent most of his time at home, resulting in higher utility expenditures and fuel expenses travelling to and from clinic appointments. In addition, one individual reported an increase in grocery shopping bills after being compelled to adjust shopping habits due to accessibility concerns and to avoid contact with other people. Consequently, these individuals believed that increased costs had added to their unexpected concerns prior to treatment.

5.9 Summary

The second embedded unit of analysis presents the findings of semi-structured interviews with 16 participants about the challenges they experienced with regards to their adherence to oral chemotherapy medicines. The participants' average age was 65.3 years, and capecitabine was prescribed as the oral chemotherapy drug to the vast majority (93.8 percent, n=15), with Trifluridine + Tipiracil (Lonsurf®) prescribed to one individual. The data revealed twelve categories centred on five broad themes that encapsulated the dimensions of adherence. The findings, which were triangulated with the results of the first embedded unit of analysis (questionnaire survey), are summarised in *Table 5.3* below.

Table 5.3 Summary of the main findings: factors influencing oral chemotherapy adherence.

	Objective	Findings
Embedded Unit of Analysis 2	Explore the challenges with adherence to oral chemotherapy medicines and identify influences on medication use among colorectal cancer patients.	<p>Theme 1: Therapy-related Factors</p> <ul style="list-style-type: none"> • Oral Chemotherapy – Dosing Regimen: <ol style="list-style-type: none"> i. Several participants felt they were used to following instructions though some described the regime as a chore or burden that could impact their longer-term adherence. There were difficulties with remembering to take twice-daily dose and some participants felt it was controlling their way of life specifically with eating and sleeping times. ii. A consistent daily routine helped some participants remember to take the medicine. Also, familiarity helped with confidence and with incorporating a consistent dosing regimen into their lives. • Adverse Effects of the Treatment: <ol style="list-style-type: none"> i. The experience of one or more treatment-associated side effects was reported by 87.5% (n=14) of the interviewed cohort. Individuals reported side effects included hand-foot syndrome, tiredness, loss of taste, diarrhoea, vomiting, infections, blood clots and mouth ulcers. ii. Several participants (25%, n=4) reported medication being stopped or paused in response to adverse effects. Cases of infection and diarrhoea were the main causes for stoppages. iii. Seven (43.8%) participants reported a reduction in dose due to side effects which positively impacted tolerance towards the medication. Additional treatment to counteract side effects was prescribed to 43.8% (n=7). Some participants underwent several changes during their treatment and experienced confusion with their medication. <p>Theme 2: Patient-related Factors</p> <ul style="list-style-type: none"> • Forgetfulness: <ol style="list-style-type: none"> i. Forgetfulness was related to medication non-adherence. A break or disruption in routine, tiredness were common reasons for forgetting a dose. Both the morning and evening doses were affected. • Ownership and Responsibility: <ol style="list-style-type: none"> i. Taking ownership was a positive feature with adherence as some participants felt it was their responsibility to ensure they followed treatment recommendation and ask for assistance when required. ii. After a few incidences with certain side effects some participants felt confident with managing those symptoms.

		<ul style="list-style-type: none"> iii. Participants referenced practical methods to help them with remembrance and self-management of medication that included: pillbox, family members, mobile alarms, coinciding tablets with eating times and keeping a daily log. • Knowledge and Understanding: <ul style="list-style-type: none"> i. Participants that had a good understanding of their oral chemotherapy medicine were more likely to view their treatment as a necessity. ii. Several participants believed that adherence to the medicine was the right thing and placed their trust in clinicians to improve their health. Other participants were unsure what to expect from the treatment and living in hope. Some individuals felt that taking the tablets was important in the spread and prevention of the disease, although the medicine would not cure them. iii. 25% (n=4) of participants described their medicine as a 'poison' arguing that was the reason for making them feel unwell. Some participants were uncertain when asked about their medicine and found it difficult to recall the reasons for being prescribed it and whether they were taking it for beneficial reasons. iv. The sources of information to obtain knowledge varied: some participants referred to clinicians at appointments and support from family members. Talking to other people with similar experiences helped with gaining more understanding. However, unverified websites and online chat forums had an undesirable impact typically when coming across side effects and negative stories from other users. • Treatment Needs and Concerns: <ul style="list-style-type: none"> i. Perseverance in times of adversity and the determination to continue with their treatment were associated with medication adherence. There was a sense of duty towards those close to them including families and the resilience brought out positive traits in their personality. There was a fear however of treatment being stopped and some participants were willing to suffer in order to receive optimal treatment. ii. Participants displaying high tolerance viewed the medicine as necessary and were willing to endure side effects to reap the benefits. Some participants reached a breaking point with tolerating side effects. The physical properties of the tablets and swallowing was a common source of disturbance. iii. Participants raised concerns about whether the treatment was effective, side effects and the long-term effects of the treatment. Participants expressed the need to live a normal life and worries were heightened in participants that were privy to other people's experiences. Concerns about long-term effects raised doubts to whether medication adherence would cause permanent damage. Also, some participants questioned whether they were taking the medicine for good reasons. • Effective Treatment Behaviours:
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		<ul style="list-style-type: none"> iv. Developing a positive attitude and staying in high spirits helped as a coping mechanism. Good experiences developed positive change in attitudes. A lack of confidence with the medicine was attributed to the distress at the start and the initial response was of caution and denial. There was a mutual dislike for medicines in participants displaying negative attitudes that were heightened by negative experiences. v. Several participants were experiencing low feelings during the treatment that was attributed to the initial shock, overthinking and side effects of the medicine. vi. Participants with family history impacted by cancer were more likely to hold negative emotions with heightened feelings of inevitability of experiencing a similar fate. <p>Theme 3: Condition-related Factors</p> <ul style="list-style-type: none"> • Co-morbidities: <ul style="list-style-type: none"> i. Half (50%, n=8) of the participants with pre-existing conditions experienced further complication in their condition or were advised to stop taking a particular medication due to drug interactions with the oral chemotherapy tablets. ii. Participants with comorbidities may vary with their views on the treatment benefits and tolerable risk of adverse effects. <p>Theme 4: Healthcare System related Factors</p> <ul style="list-style-type: none"> • Knowledge and Skills Transfer: <ul style="list-style-type: none"> i. There were differences in participant preference about the education session provided at the start of the treatment. Some preferred basic information while others a more detailed understanding. The experience was overwhelming at the start for some participants who found it difficult to absorb information. ii. The level of engagement among participants varied. Participants that engaged with their treatment were more aware about medication use and increased likelihood of adherence. iii. Participants that were engaged with their treatment were more likely to be more open to discussing changes or side effects of the treatment with their clinician though some were unsure about how to approach the subject about shared decision making. iv. The influence of the MCT on medication adherence was unclear yet participants preferred to be assessed by their doctor as opposed to other healthcare clinicians. Participants expressed satisfaction with the clinical support provided by the wider MCT though it was evident that a large proportion of Participants viewed their doctor as the focal point with an authoritative role in their treatment plan. • Development of Healthcare Services:
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		<ul style="list-style-type: none"> i. Several participants raised concerns about the interaction time with clinicians and limited accessibility to discuss their issues. Participants deduced the heavy workload and staff shortages as reasons for short consultation times and availability. ii. Some participants felt there was a difference in follow-up care received with taking the oral chemotherapy medicine compared to the care post-surgery. iii. Waiting times at the outpatient clinic for appointments and prescriptions were reasons given by participants for not disclosing ongoing issues with their treatment. <p>Theme 5: Social and Economic related Factors</p> <ul style="list-style-type: none"> • Support Network and Social Impact: <ul style="list-style-type: none"> i. Participants with family support during treatment felt they played an important role with medication adherence. They also catered for their emotional and physical needs. ii. For individuals who lived alone, family/friends support had a different role since they preferred to approach their family about their requirements as they were more comfortable making their own decisions. iii. Participants were aware of who to contact for clinical support with their medicine. iv. Over half of participants stated that the treatment had negatively impacted their social life for various reasons included side effects and low feelings. Some participants made lifestyle changes after experiencing adverse effects with alcohol. • Economic Impact: <ul style="list-style-type: none"> i. Over a third of participants revealed they had incurred some loss in income since starting the oral chemotherapy medication. ii. Participants experienced financial difficulties due to being off work, taking early retirement and with travel costs to and from clinic appointments. Participants that were on state benefits expressed incurring extra costs with house utilities and groceries.
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Chapter Six

Discussion

6.1 Introduction

The aim of this research was to explore the factors that influence colorectal cancer patients' adherence to oral chemotherapy medicines in South Wales. The patient's sociodemographic status, medication adherence scores, and beliefs about treatment were each examined in the study.

The chapter commences by highlighting the contribution this research makes to understanding medication adherence in CRC care. Divided into interrelated sections, the findings are then discussed within the context of the available literature. This chapter goes on to consider the implications for policy, clinical practice, and research. The study's strengths and limitations, dissemination plan, reflexivity, and conclusions are also described.

6.2 Key Findings and Knowledge Contribution

- Almost two-thirds of the interviewed cohort reported negative emotions (e.g., low feelings). As this study has identified contributing factors including medication side effects, initial distress after learning about treatment needs, forgetting a dose, and malaise about whether the medication would work, healthcare clinicians should acknowledge the link between psychological distress and difficulties with medication

adherence and actively assess this during consultations. Developing a pre-screening tool to identify medication-related issues and psychological distress may help those most in need of additional information, education, and support for adherence.

- Medication non-adherence was predominantly related to forgetfulness and the adverse effects of oral chemotherapy agents. Participants perceived oral chemotherapy-related side effects to be distressing and limiting in their ability to live a normal life, which affected their attitudes and medication-taking behaviours. This study suggests that poor management of side effects may have a greater impact on oral chemotherapy drug adherence in CRC patients than the occurrence of adverse effects alone.
- The findings identified knowledge deficits that could unintentionally impact adherence. CRC patients who were less well informed had difficulty recalling the purpose of the tablets, understanding how the medication worked, or deciding whether they were taking them for the right reasons. In addition, nearly one-third of the participants conducted their own research using online sources. Participants described using online sources to learn more about the side effects, and would internalise this information, which could influence their adherence decisions. However, little is known about how health information research using online sources influences adherence to oral chemotherapy medications.
- High MARS scores were reported, indicating high adherence to oral chemotherapy agents. It is acknowledged, however, that the MARS measure used in this study was an adapted and unvalidated tool for the CRC target population. Consideration should be given to developing a scale that is more specific for measuring CRC patients' adherence to oral chemotherapy medicines.

- To the researcher's knowledge, this is the first study to assess CRC patients' oral chemotherapy medication adherence scores across sociodemographic groups that considers multiple levels of deprivation. Preliminary analysis indicated a statistically significant difference in adherence between the most deprived areas (Q1: 53.3%, n=8) and the least deprived (Q4: 73.7%, n=14). To support the tentative results, more research with a larger sample would allow for a more robust statistical analysis of the MARS items' ability to discriminate across WIMD categories of deprivation.
- The BMQ indicated that patient beliefs in the necessity of treatment outweighed their concerns (99.3% vs. 44.1%). Nevertheless, the study findings indicated that CRC patients were concerned about medication side effects and their long-term implications, the administration of oral chemotherapy agents and swallowing difficulties, and the negative treatment beliefs of individuals with a family history of cancer.

6.3 Assessing Adherence to Oral Chemotherapy Medicines

The MARS scores revealed that 64.4% of patients achieved 100% adherence to their oral chemotherapy medicine (MARS score = 40). However, only 5.1% of study participants had MARS scores below 90%, indicating high adherence to oral chemotherapy agents. These results are similar to those of other studies reporting high adherence among colorectal cancer patients receiving oral chemotherapy treatment (Simons et al. 2011; Winterhalder et al. 2011; Krolop et al. 2013; Figueiredo Junior and Forones 2014; Walter et al. 2014; Bourmaud et al. 2015; Sugita et al. 2016; Le Saux et al. 2018).

The high MARS scores shown by the self-reported method may reflect issues with how adherence is measured in this patient population rather than true high adherence. In fact, there have been previous reports of adherence issues with oral chemotherapy agents. Hefner et al. (2017) reported an adherence rate of 51% using the Basel Assessment of Adherence Scale (BAAS) for CML patients receiving oral TKIs. Ziller et al. (2009) reported a MPR of 69% for breast cancer patients on anastrozole. This study's use of an adapted version of the MARS scale (Horne and Weinman 1999; Cohen et al. 2009) is a potential confounding variable. Two items were removed from the MARS scale following a pilot run to determine its usefulness and relevance for assessing CRC patients receiving oral chemotherapy medicines (see *section 3.5.3.1.2*), resulting in an eight-item scale. However, the study acknowledges that the lack of revalidation of the scale is a limitation. This should be taken into consideration, and only tentative conclusions can be drawn from the study findings.

Additionally, the sample lacked diversity because the study participants were mostly elderly (average age: 65.7 years) and all of them were of white ethnicity. Earlier studies have shown large variations in cancer survival by race and ethnicity (Ward et al. 2004) and these characteristics were also associated with adherence to endocrine therapy in a review of breast cancer patients' (Megan C Roberts et al. 2015). The lack of ethnic diversity may be explained by the fact that 93.2% of South East Wales residents identified as white in the most recent equality and diversity statistics report (Welsh Government 2022). The proportion of those who identify as white increases with age, reaching 98.9% among those aged 65 and older. In addition, CRC can develop in young adults and adolescents; however, the majority of CRC diagnoses in Wales occur in people aged 50 or older (WCISU 2015). The representation of different ethnicities is important because they may face unique challenges to care, such as the impact of cultural influences on their perceptions of medication adherence, socioeconomic issues, or access to the healthcare system or providers. Future studies should therefore involve subgroup analysis using a diverse UK-wide patient population. The limitations of this study and adherence measurement are described later in *section 6.10*.

According to the MARS self-report questionnaire, 35.6% of patients were non-adherent to one or more of the MARS statements. Forgetting to take a dose, as reported by 28.8% of patients, was the most common reason for unintentional non-adherence among the MARS statements. This aligns with the findings of other studies (Simons et al. 2011; Winterhalder et al. 2011; Bhattacharya et al. 2012; Krolop et al. 2013; Timmers et al. 2016; Chen et al. 2020). According to Atkins et al. (2006), participants found it more socially appropriate to disclose unintentional than intentional behaviours, such as skipping a dose. Interview findings

identified that just under two thirds of patients (62.5%, n=10) admitted forgetting to take at least one dose of their medicine during their treatment. Although oral chemotherapy agents have several advantages, including great flexibility and convenience for the patient and minimal disruption of daily activities (Schneider et al. 2014a; Peng and Wu 2020), CRC patients in this study found it difficult to remember to take their oral chemotherapy medications when there was a disruption in routine, such as socialising, attending clinic appointments, or being in a rush. Remembering to take a medication dosage following a disturbance in routine required a great deal of self-discipline and was one of the main reasons individuals forgot to take their medicine. In line with this finding, the highest treatment concern in the BMQ survey revealed that 40.7% (n=24) of participants believed that the oral chemotherapy medication caused disruption in their lives.

Practical methods were an effective tool for CRC patients to support them with self-managing their oral chemotherapy medications. Several individuals in this study (> 40%) referred to practical methods that included the use of medication or pill boxes, setting mobile alarms for morning and evening doses, coinciding tablet intake with eating times, and family members that were actively involved in their treatment regime. Reminder systems initiated by CRC patients can reinforce the medication-taking behaviour more effectively than education alone. Setting multiple mobile alarms, for example, not only worked to prompt patients with dosing times, but its other function for patients with other health conditions was the ability to distinguish between different dosing periods. Timmers et al.'s (2016) study found that over 60% of patients used a reminder system to help them remember to take their capecitabine medication. In research conducted by Lecouturier et al. (2011), individuals who used pillboxes

reported less disruption in their lives and greater control over the organisation and administration of their medication and condition. It is recommended, however, that care be taken to ensure that the oral chemotherapy medications are identifiable when stored in pillboxes (with drug name and dosage) so that they are not mistaken for other medicines (Burhenn and Smudde 2015). In addition, studies on the use of mobile applications to promote adherence to oral chemotherapy agents and self-management of complications associated with their use have demonstrated their usefulness (Weaver et al. 2014; Fishbein et al. 2017; Magalhães et al. 2020). Clinician-initiated reminders, like the randomised control trial by Spoelstra et. al (2016) of a mobile nurse-led health intervention using text messages, helped to increase adherence in 75 patients taking oral anticancer agents. But as technology evolves to promote CRC patients' adherence, more research is needed to address how well such applications work in a clinical setting before its implementation.

6.4 Treatment Toxicity and Adverse Effects

Despite the safety profile of oral chemotherapy agents (capecitabine and trifluridine–tipiracil), the proportion and severity of toxicities (grade 3 or 4 adverse effects) is still an important issue. The vast majority (88%) of CRC patients in this study reported experiencing one or more oral chemotherapy-related side effects. Hand-foot syndrome (HFS), constant tiredness or fatigue, loss of taste, diarrhoea, nausea, and vomiting were the most frequently reported adverse effects. Previous studies have also reported comparable oral chemotherapy-induced side effects (Simons et al. 2011; Winterhalder et al. 2011; Bhattacharya et al. 2012a; Krolop et al. 2013; Figueiredo Junior and Forones 2014; Walter et

al. 2014; Bourmaud et al. 2015; Sugita et al. 2016a; Timmers et al. 2016; Le Saux et al. 2018b; Chen et al. 2020). Tiredness had a negative impact on behaviour and was indicated by 56.3% of interviewees as one of the main reasons for cutting back on social activities. This was a source of frustration. Tiredness and/or fatigue were also the leading causes for forgetting the evening dose. This is consistent with the findings of the Fernandez-Ribeiro et al. (2017) study, which indicated that fatigue was the most limiting factor with the highest impact on mood. Some individuals in this study felt they had reached their breaking point with their medication because the persistent fatigue was wearing them down and taking away some of their independence. This made it difficult for them to adapt to living a normal life. The psychological aspect, according to Lebovits et al. (1990), may jeopardise adherence by provoking intake-reducing behaviours or even the temporary stopping of medication.

Previous randomised phase 3 clinical trials have documented the side effect profile of oral chemotherapy agents reported by CRC patients in this study as commonly reported adverse effects (Van Cutsem et al. 2001; Hoff et al. 2001; Mayer et al. 2015). The findings of this study suggested that individuals perceived side effects to be distressing and limiting to their quality of life, which affected their attitudes and behaviours regarding the oral chemotherapy treatment. Nonetheless, even after dose reductions, three individuals showed high tolerance and were determined to adhere to the treatment and endure adverse effects because they believed it was necessary to their survival to prevent a relapse of their condition. This finding is consistent with research by Bourmaud et al. (2015). These researchers found that patients had high expectations for the efficacy of the oral capecitabine treatment. As a result, they developed their own strategies to manage side effects and were hesitant to inform their

oncologist about these side effects for fear of having their treatment discontinued. According to Haller et al. (2008), differences in the tolerability of oral capecitabine may be attributable to a range of potential factors, such as cultural differences in patients' behaviour for orally administered drugs, including their willingness to continue taking medication despite experiencing side effects. In this context, cultural differences refer to variations in patients' beliefs, values, and attitudes towards illness and treatment, which can be influenced by factors such as ethnicity, religion, and social norms. For instance, the findings in this study suggested that some CRC patients considered it their responsibility to adhere to the oral chemotherapy medicine as part of a moral obligation to their families, whereas in other cultures, patients' may prioritise avoiding discomfort or preserving their quality of life. These cultural factors may influence CRC patients' perceptions of the benefits and risks of treatment and their decision-making regarding adherence to medication.

This study suggests that poor management of adverse effects may have a greater influence on oral chemotherapy drug adherence and quality of life in CRC patients than the mere presence of adverse effects. There were several factors related to adverse effects that may contribute to nonadherence: for instance, negative emotions, malaise about the treatment, reduction in social activities, concerns about the long-term effects, and treatment interruptions. Confusion induced by additional prescribed medications and/or dose changes may also increase the possibility of CRC patients misidentifying the oral chemotherapy medication to take at the appropriate times. In addition, poor management of adverse effects may contribute to treatment toxicity. The findings reported that 25% of CRC patients had their oral chemotherapy treatment stopped or paused, and 43.8% had dose reductions due

to exacerbation of pre-existing health conditions. Treatment-related toxicity can lead to dose reductions (Van Cutsem et al. 2001; Hoff et al. 2001) and has been shown to influence discontinuation rates and adherence among CRC patients (Winterhalder et al. 2011; Kovacic et al. 2017; Muluneh et al. 2018). According to Muluneh et al.'s (2018) study on patients' perspectives on the use of oral chemotherapy medicines, one of the primary reasons for over a third of patients cutting back was side effects, with HFS and fatigue being the most commonly cited explanations.

Furthermore, timely management of unwanted effects throughout the treatment term as well as education of CRC patients on early detection of signs and symptoms, may improve their experience and, thus, medication adherence. Several individuals in this study felt that they were able to tolerate the medication better after a medical intervention and/or dose reduction, which had a positive impact on their attitude toward the treatment. This suggests that when treatment is reduced to manage toxicity, two things happen: first, the risk of severe and life-limiting toxicity is lowered, and second, adherence is likely to be supported because fewer side effects will be experienced. The presence of side effects did not have a significant impact on adherence, according to the findings of Geissler et al. (2017), who studied adherence influencing factors in CML patients in 63 countries. However, there were major differences between patients who reported their adverse effects were well-managed (40.9% had high adherence) and those who did not (24.2% had high adherence). In line with these findings, Eliasson et al. (2011) concluded that overcoming adverse effects facilitated adherence to imatinib, an oral small molecule inhibitor used in the treatment of CML. Several studies (Molassiotis et al. 2009; Weaver et al. 2014; Visacri et al. 2022) have tested the

effectiveness of symptom-focused interventions in patients with CRC and breast cancer treated with oral capecitabine. In the Molassiotis et al. (2009) homecare program, 164 patients were randomly assigned to receive either the nurse-led program or standard care for a period of 18 weeks. The homecare program was able to help patients manage the adverse effects (e.g., diarrhoea, nausea, and fatigue) by conducting weekly toxicity assessments. Therefore, identifying unwanted effects early and using patient-specific intervention programs to monitor their care may help ease symptoms that could cause them to stop taking the oral chemotherapy medicine.

6.5 Socioeconomic Deprivation and its Influence on Medication Adherence

An interesting trend observed in this study was the potential disparity in adherence scores among different WIMD deprivation quartiles in South Wales. While the findings are based on preliminary analysis and a small sample size, they suggest a possible association that warrants further investigation. Notably, the preliminary analysis indicated a statistically significant ($p=0.0002$) difference in adherence between the most deprived areas (quartile 1: $n=8$, 53.3%) compared to the least deprived areas (quartile 4: $n=14$, 73.7%). These findings provide initial support for the theoretical proposition between lower adherence and patients from lower sociodemographic areas (see *table 3.1*). This is the first time an empirical study has shown a disparity between adherence scores and different WIMD deprivation quartiles for people taking oral chemotherapy agents for CRC. However, it is important to note that these conclusions remain tentative, as a larger sample is necessary to conduct a more robust

statistical analysis and evaluate the MARS items' capacity to differentiate between WIMD categories.

According to the WIMD data, participants who were having financial hardships predominately resided in the most deprived areas (quartiles 1 and 2). In addition, almost a third of the interviewed cohort revealed they had experienced financial difficulties and had incurred some losses in income since starting the oral chemotherapy medication. Evidence suggests that higher financial status and a better socioeconomic position have a positive impact on adherence among patients with chronic diseases and patients' taking oral anticancer drugs (Gast and Mathes 2019). It has also been reported that patients with part-time jobs performed better with adherence than those who do not work, with the increased income reducing the burden of medical treatment costs (Kapoor et al. 2015). Other research, on the other hand, found that a patient's job status and professional obligations were linked to a higher likelihood of poor adherence (Bourmaud et al. 2015; Chen et al. 2020). In addition, patients who are employed have been shown to have a statistically significant association with medication non-adherence (Hirao et al. 2017). Nonetheless, medical treatment costs and the requirement for health insurance do not apply to NHS prescriptions in the UK, as reported in prior studies. Participants in this study faced financial hardship for a variety of reasons, including long periods out of work, early retirement, and out-of-pocket expenses, all of which may have increased their risk of nonadherence, as individuals did not wish to extend their treatment beyond the 6-month cycle. Zivin et al.'s (2010) study on the factors associated with cost-related nonadherence in older patients suggested that factors such as overall depressive mood can influence adherence when patients are under financial pressure.

Consequently, CRC patients who report financial difficulties may be expressing more general concerns about their therapy, which might be addressed through improved patient education and an open dialogue with clinicians about the medication's necessity or risk of side effects.

Financial issues and their impact on CRC patients' adherence decisions are intertwined with other socioeconomic factors, such as the function of the family and social support system. According to evidence, CRC patients who live with their parents or who have family obligations are at a higher risk of poor adherence and efficacy (Bourmaud et al. 2015; Chen et al. 2020). In contrast, 81.3% of interviewees in this study lived with family, and several of them felt their support played an important role with medication adherence because family members actively reminded patients about their doses and served as useful information sources about their medication and condition. This is consistent with previous adherence studies with oral anticancer drugs (Given et al. 2011; Efficace et al. 2012; Mathes et al. 2014). Efficace et al.'s (2012) study suggested that a higher level of social support (from family members, friends, and significant others) and satisfaction with information received about the therapy were two of the most important characteristics associated with optimal adherence to long-term imatinib treatment among CML patients.

Clinicians may need to be mindful of risk factors for non-adherence, i.e., living alone, considering the findings of this study. Firstly, 18.8% of the interviewed cohort lived alone, and the MARS survey revealed that none of them were adherent to the MARS statement, "*I decide to miss out a dose*". In addition, the MARS data showed that these individuals were likely to forget to take their oral chemotherapy medication and to skip doses. Similarly, Xu et al. (2012)

found that in 116 breast cancer patients', individuals with limited social support had lower tamoxifen adherence. The findings in this study suggested that individuals who lived alone were less communicative and willing to discuss their adherence decisions. In addition, they preferred to deal with their own issues and only consulted family members when necessary; hence, less effective support and a lack of understanding of the disease may have contributed to lower medication adherence. Furthermore, two individuals were less engaged in discussing adherence-related issues. For instance, one individual frequently elected not to take oral capecitabine on the same day as IV oxaliplatin therapy to avoid combining the two forms of chemotherapy. Participants felt they avoided having conversations about adherence issues to avoid burdening their clinicians and because of access issues in order to prevent further clinic delays. Increased appointment time has been recommended as a way to strengthen discussions between healthcare professionals and patients (Welsh Government 2016). Poor engagement with the medical system may be an important factor in treatment adherence (Sedjo and Devine 2011), but additional consultation time may allow healthcare professionals to inquire about adherence decisions and allow patients to ask questions, which may alleviate some patients' anxiety. It may also aid in the development of stronger patient-provider relationships, as patients may be more willing to discuss adherence concerns that can be addressed through more open discussions about their treatment needs. Even though a small percentage of CRC patients demonstrated non-adherence, even at low levels, the clinical impact could be significant because oral chemotherapy dosing is precisely calibrated based on surface area, and slight deviations can result in sub-optimal outcomes and treatment failure.

6.6 Psychological Distress

Among the influences associated with adherence, the patient's psychological distress is critical. Although this study did not use tools to assess depression, the findings revealed that 62.5% of participants reported negative emotions (e.g., low feelings), which were brought on by a variety of factors such as medication side effects, initial distress after learning about their treatment needs, forgetting a dose, and malaise about their condition. Health anxiety has been described as the fear and worry that arise in response to living with a chronic condition and consists of distressing emotions (e.g., fear), thoughts of danger, and perceptual and behavioural features (Jones et al. 2012; Lebel et al. 2020). Indeed, a recent analysis revealed consistent evidence across chronic diseases that health anxiety is common, impacting over 20% of patients in most of the illnesses evaluated (Lebel et al. 2020). This study identified, for instance, that two participants who felt strongly about forgetting a dose (distressing emotions such as fear and apprehension) exhibited indicators of medication overuse, with the assumption that adding missed doses to the end of the treatment term would not significantly affect treatment outcome. This was consistent with findings from Bender et al.'s (2014) study that explored the influence of patient and treatment factors on breast cancer patients' adherence. The Bender et al. study found that a low mood and the presence of symptoms prior to starting therapy predicted nonadherence to endocrine medication over time. The degree of people's negative emotions increased with time because of how they felt about their finances, their symptoms, the stage their condition had reached, and their intricate dosing regimens. Furthermore, Le Saux et al. (2018), investigating the potential safety implications of capecitabine over-adherence, reported high adherence with pill-count and MEMS use, suggesting that this was due to over-adherence because patients were more

concerned about the severity of their disease and, as a result, were more likely to take medications when they shouldn't. Fear of disease and/or adverse effects and the risk of over-adherence are relevant issues for CRC patients' and healthcare providers, as oral chemotherapy dosing is often quite complex. Cognitive (i.e., ideas, beliefs) and emotional (anxiety, fear, denial) components related to the oral chemotherapy drug and illness severity have a considerable influence on psychosocial aspects of oral chemotherapy adherence (Kaptein et al. 2021). It is perhaps individuals who are emotionally distressed through treatment that are most at risk of non-adherence.

Moreover, a study investigating the predictors of non-adherence to aromatase inhibitors (AI) among breast cancer patients found depression to be a statistically significant factor, with patients showing higher non-adherence rates (Sedjo and Devine 2011). Sundbom and Bingefors' (2013) study that evaluated the association between self-reported anxiety and/or depression using the Hospital Anxiety and Depression Scale (HADS) revealed that patients experiencing psychological distress have a higher risk of intentional and unintentional non-adherence. The authors suggested that patients are likely to make an active decision to be non-adherent when they are experiencing symptoms of anxiety and/or depression. In this study, some individuals coped with low feelings by opting to break the mould by making changes in their lives, such as taking up hobbies like house renovations, which elicited positive emotions. These activities stopped them from overthinking by bridging the gap created by having more free time. In other instances, participants sought medical advice, and a temporary increase in anti-depressant medication improved their mood and general wellbeing. Nonetheless, several individuals were not accustomed to experiencing such low

emotions as those associated to depression and/or anxiety. For instance, 25% of interviewees in this study developed feelings of hopelessness and indicated signs of withdrawal, distancing themselves from family and friends. These individuals were hesitant to discuss medication adherence issues because they did not want sympathy or to bother others by sharing their issues. Lebovits et al. (1990) investigated nonadherence with self-administered cancer chemotherapy (oral cyclophosphamide and prednisolone) in 51 breast cancer patients and discovered that nonadherent patients had considerably higher depressive symptom disturbances. Thus, it is important to screen CRC patients' taking oral chemotherapy agents for psychological distress in a timely manner, as these indicators may support medication adherence. In order to identify and resolve medication adherence issues in a clinical setting, Weinman et al. (2019) created a brief pre-consultation screener that integrated a medication beliefs questionnaire and an adherence self-report scale. Instead of directly asking patients about their adherence, the screening tool asked them to indicate whether they were having problems that might be indicative of non-adherence. According to the authors, the screening tool would assist clinicians in identifying medication-related issues and indicators of non-adherence so that they could be openly discussed and resolved. Therefore, the development and implementation of a screening tool for CRC patients may identify individuals most in need of additional information, education, and support for adherence.

6.7 Assessing Treatment Necessity and Concerns

Treatment beliefs were obtained from the Beliefs about Medicines Questionnaires (BMQ) (n=59), and consistent with the literature (Bhattacharya et al. 2012; Timmers et al. 2016), the scores indicated that patient beliefs in the treatment necessity (99.3%) outweighed their

concerns (44.1%). This balance in terms of treatment necessity has been linked to better adherence (Horne and Weinman 1999; Horne, Sarah C E Chapman, et al. 2013), which could help to explain the high adherence scores. In addition, a recent study reported that patients who perceived greater benefits were more likely to show good adherence (Chen et al. 2020). It has also been suggested that people with cancer may have higher adherence than people with other chronic diseases because cancer patients are highly motivated by the gravity of their disease and have too much to lose by being non-adherent (Waterhouse et al. 1993; Winterhalder et al. 2011). The findings suggested that CRC patients who believed their treatment was necessary displayed features of determination and persevered to adhere to oral chemotherapy treatment in the face of hardship, particularly with adverse effects, since they believed they had much to live for and hoped for a positive treatment outcome. The inner resilience required during the treatment was a test of character for some, and they dealt with it by setting out small, achievable goals for each treatment cycle.

According to theories such as social cognitive theory and the extended health belief model, self-efficacy has a direct influence on patients' necessity-concerns beliefs. Self-efficacious individuals are more successful at taking medication because they are more inclined to persevere under tough conditions (Holmes et al. 2014). A study by Gonzalez et al. (2007) evaluated the levels of HIV medication adherence and beliefs about the medication and reported that adherence is higher among patients who are confident in taking their medication and have fewer concerns about side effects. The BMQ survey in this study revealed that 81.3% of respondents held strong beliefs that their health in the future was dependent on the success of the oral chemotherapy medicine. Participants believed adhering

to the medicine was the right thing to do and that putting their trust in healthcare clinicians to look out for their best interests would lead to better health. Looking to the future in hopes of resuming a normal life, as well as a sense of duty to their families to complete the therapy, were key motives that emerged from the findings. As discussed in *section 6.4*, however, there was a subgroup of patients who had a high tolerance for the medication's side effects and were hesitant to discuss the issue with their healthcare providers out of fear that their medication would be interrupted or discontinued because they had a strong need to avoid a relapse. Consequently, it appears that there is a subgroup of patients who push too hard, and paradoxically, the reverse of what they want can occur.

Twenty-five percent of the interviewed cohort reported having a family history of cancer that was treated with chemotherapy but proved fatal; as a result, they tended to hold negative beliefs about the medication. A study that looked at the relationships of family history-related factors, causal beliefs, and mammography screening adherence discovered that women who perceived a higher importance for family history in illness risk were more likely to adhere to mammography screening (Hong et al. 2020). In addition, Brito et al. (2014) found that breast cancer patients with a family history of cancer had a higher likelihood of adhering to hormone therapy. The differences in behaviour could be attributed to malaise about the treatment success, hereditary risk factors, and initial emotional distress after learning about treatment needs, which created uncertainty for CRC patients who did not wish to experience a similar fate.

Moreover, the BMQ concerns survey revealed that 23.7% of respondents had treatment concerns regarding the oral chemotherapy medication. Some individuals were concerned about the administration of oral chemotherapy agents, which was regarded as a physical barrier to medication adherence. The findings suggested that individuals were concerned about the size of the tablets and because of their previous experiences with swallowing reflexes. This is in accordance with previous literature on oral chemotherapy agents (Krolop et al. 2013; Verbrugghe et al. 2013b; Chan et al. 2020; Talens et al. 2021). Negative emotions, such as anxiety about ingesting large tablets and choking fears, may be elicited, which can have the potential to impact adherence. As previously indicated, medication-related issues such as physical concerns could potentially be detected in a pre-screening tool, as oral chemotherapy agents for CRC patients are only effective when consumed.

6.8 Knowledge of the Oral Chemotherapy Medication and the Information Sources

According to the BMQ-N survey, 84.7% of respondents held strong beliefs with the statement, *“my medicine protects me from becoming worse”*. The interview findings suggested that participants who considered their treatment necessary were inclined to have a good understanding of the importance of oral chemotherapy medication, were eager to learn about the treatments’ benefits and side effects to develop their knowledge, and asked questions to clinicians to seek clarification. Bassan et al. (2014) suggest that patients’ knowledge, understanding, and recall of information regarding oral chemotherapy agents are likely to influence adherence behaviour, and patients’ must learn new skills (i.e., health literacy), such as remembering daily intake schedules, following instructions, and avoiding certain foods, in order to manage taking oral chemotherapy medication at home.

Several participants felt that the tablets were important in the prevention and spreading of the disease, but that a balance had to be achieved between the dosage and the potential for harm. In line with the findings of Yagasaki et al.'s (2015) qualitative study, gastric cancer patients experienced an inner conflict between rational belief and emotional resistance to medication adherence due to encountering doubt regarding efficacy and concerns over potential harm associated with the agent's use. Bourmaud et al. (2015) found that patients routinely overestimated the balance between the advantages and disadvantages of oral chemotherapy treatment. The authors reported that patients underestimated the risk of the side effects and that there was a misconception about the treatment's efficacy that increased over time. In this study, for example, a quarter of the interviewed cohort believed the oral chemotherapy agent was a "*poison*"; this belief was thought to be the root of the side effects that suggested the treatment was indeed effective. This misunderstanding about the treatment's efficacy highlighted a knowledge gap about the mode of action of oral chemotherapy agents, as such views may discourage patients from reporting adverse effects promptly, which could unintentionally impact adherence.

According to the survey sample, over a quarter of respondents had no formal education, and just about 15% had a higher education degree. The findings suggested that individuals who were less well informed had difficulty recalling the purpose of the tablets, understanding how the medication worked, and determining whether they were taking them for beneficial reasons. Marks et al.'s (2010) study compared patient demographics and health literacy with respect to medication knowledge, and the findings indicated that health literacy plays a major

role in comprehending the names, dosages, indications, and potential side effects of one's medications. Being more aware of the disease and treatment, as well as having at least a secondary school education, were all linked to improved adherence behaviour in CML patients receiving imatinib therapy (Noens et al. 2009). As a result, identifying individuals with low health literacy would allow for the targeting of more suitable patient education initiatives to increase their awareness of their therapy and, consequently, may improve treatment outcomes.

An important finding from this study is the sources of information used by participants to obtain knowledge about their oral chemotherapy medication. A recent study by Muluneh et al. (2018) reported that the three most frequent sources of general information about their oral chemotherapy medication that patients identified were their physicians (70%), the medication label (60%) and their pharmacist (36%). In addition, work by Diaz et al. (2002) to determine patients' use of the internet for medical information determined that 53.5% made use of online sources, with those using them more likely to be educated and have higher incomes. In addition, 59% of those using the internet for health information did not discuss this information with their doctor (Diaz et al. 2002). The interview findings of this study revealed that while some patients solely sought information from their healthcare clinicians (25%), others turned to sources such as relatives and friends (37.5%) who had gone through similar experiences or by conducting their own research using online sources. Interestingly, almost a third of the participants (31.25%) mentioned using the internet to find out health related information about their treatment. Before starting the oral chemotherapy treatment, participants stated they had received patient information leaflets with general information

about the medicine from a patient education session. However, because they were either out of work or retired, participants said they had more spare time on their hands and spent it researching their medicine.

The internet's open and unmediated nature creates questions and concerns about the quality and authenticity of the information available (Arbuckle et al. 2019). The availability of such enormous volumes of data may also encourage people to form their own judgments about a medicine without having to speak with a healthcare provider directly (Diaz et al. 2002). This was in keeping with the findings in this study when participants described using online sources to learn more about the side effects, which manifested into negative doubts. It was clear, however, that some participants would seek clarification from their clinicians and ask questions, while others would internalise this information, which could influence their adherence decisions. For instance, one participant who was non-adherent had negative feelings that influenced his thoughts and behaviour after joining an online community forum for patients and family members with similar diseases who had either received or were undergoing chemotherapy treatment. Many of the comments were negative, describing their struggles with the treatment or incidents in which the individuals had died, leaving him with little confidence in his medication. Although online resources can be a valuable source of information, unreliable sources can have the opposite effect, discouraging patients from adhering to their oral chemotherapy medications.

6.9 Implications for Policy, Practice and Research

Although only tentative conclusions can be drawn from the results, to reduce health disparities, clinicians should take an interventional approach to patients from deprived communities experiencing negative emotions, targeting areas such as medication beliefs, financial and welfare support, individuals with limited family and social support, and health awareness with patients who lack understanding of their treatment. This may be addressed through improved patient education and open communication with CRC patients regarding their treatment. Charitable organisations that provide community care support may be able to provide regular contact to check on their wellbeing, as well as emotional and financial assistance. Online support groups or forums have the potential to provoke negative emotions that can discourage patients from medication adherence, so the holistic approach provided by community care support groups may play a bigger role in helping CRC patients cope with taking medication on a regular basis. Further work should also examine the role of socioeconomic factors such as financial burdens and family or social support systems on patient adherence decisions in more deprived areas. Low socioeconomic status was associated with lower adherence in breast cancer patients (Megan C. Roberts et al. 2015). Although two studies identified that clinical and sociodemographic factors were not significantly associated with capecitabine adherence (Krolop et al. 2013; Kawakami et al. 2017). However, there is still limited research on the impact of socioeconomic factors on adherence, particularly among CRC patients. Social and economic pressures may take precedence over medication adherence, which could lead to suboptimal outcomes.

Healthcare providers should be aware of the link between psychological distress and difficulties with medication adherence. Clinicians should be on the lookout for early indications of psychological distress, such as unhelpful patterns in beliefs, mood, and behaviour. It may, however, be difficult for healthcare clinicians to objectively measure psychological distress and assess the severity of symptoms using the MARS scale, such as anxiety or depression, the severity of side effects, and social support. It has been noted in some studies that there is a gap between how medical professionals and patients perceive adverse effects, and there is no consensus on how to distinguish between an individual's normal fears and concerns from clinical ones (Hirao et al. 2017b; Lebel et al. 2020). For example, swallowing difficulties and their association with past trauma or the low feelings associated with oral chemotherapy treatment may result in poor coping, including challenges with medication adherence and the adoption of counterproductive lifestyle behaviours (e.g., withdrawal, reduction in social activities and interests). In addition, poor physical health caused by the adverse effects of oral chemotherapy agents can lead to poor mental health (M R DiMatteo et al. 2000). Therefore, there is perhaps a need for a pre-consultation screening tool that can identify people with risk factors for non-adherence and who are experiencing negative emotions relating to the treatment.

Developing a pre-screening tool for CRC patients taking oral chemotherapy agents is important because clinicians may use this information to identify patients' most in need of adherence support. In addition, clinicians could make use of available behavioural resources by exploring illness perceptions (Horne and Weinman 2002d) and medication beliefs (Horne and Weinman 1999), since they have important implications for medication non-adherence,

and it is critical to support CRC patients in identifying these behavioural patterns. It may also be feasible for medication adherence to improve when CRC patients gain relief from their psychological discomfort.

CRC patients should be made aware of how to recognise potential side effects early on, as timely management of existing side effects may help with preventing non-adherence to the oral chemotherapy medication. There is also a need for greater patient information on how patients can recognise whether treatment side effects are subsiding (i.e., long-term effects) and how long it will take to fully recover from the adverse effects. CRC patients' view side effects as distressing and restrictive to their quality of life, which may influence their medication-taking behaviour. Existing research focuses on the chemotherapy-induced side effects of oral treatment, but it rarely considers the longer-term consequences. Healthcare clinicians should engage with patients on symptom management decisions regularly to identify the subgroup of patients who are likely to have a high tolerance and to implement effective interventions and support systems early on to avoid treatment toxicity. Developing a pre-screening tool may enable the early identification of CRC patients with strong treatment necessity beliefs who are more prepared to tolerate adverse effects. Furthermore, identifying patients' who received oral chemotherapy agents in combination therapy and who received treatment for different intent (i.e., curative vs adjuvant treatment) should be taken into account. This is because the experiences of CRC patients are likely to be influenced by these elements, and consequently, their adherence behaviours may be affected.

Schneider et al. (2014) conducted a randomised controlled trial to test the effectiveness of tailored nurse coaching interventions to promote adherence to oral chemotherapy agents via regular phone calls. These researchers found the intervention to be beneficial with regards to helping patients manage symptoms and ensuring that oral chemotherapy medication was taken safely. As a result, tailored interventions and medication use reviews by multidisciplinary care teams may help with improving patients' adherence to oral chemotherapy medicines. It may also help patients remember to take their medication as prescribed and identify adverse effects of the medication sooner. As discussed in *section 6.3*, using practical reminders can be a more effective tool to promote adherence and reinforce medication-taking behaviour than education alone. Setting attainable goals for each cyclic treatment may also boost patient motivation and facilitate medication self-management at home. To keep patients informed, clinicians should first establish open communication with CRC patients to identify what they already know and to understand how the oral chemotherapy medication fits their lifestyle in order to determine potential solutions. CRC patients should also be provided with emotional support, especially during the first two cycles of treatment. This is because of the initial emotional distress upon learning about their treatment needs, especially if they have no prior treatment experience or have felt trauma, such as a family history of cancer.

Clinicians should be mindful of patient preferences, as this study has shown that patients have differing views on how drug information should be delivered. Some individuals preferred a positive approach at first, focusing on the positive aspects to gain confidence in taking the medicine on a regular basis, whereas others expressed their willingness to participate in the

decision-making process and preferred a detailed approach to their treatment. Shared decision-making is conceptually and practically difficult; nonetheless, according to Horne et al. (2005), a crucial aspect of shared decision-making is that patient' beliefs and preferences are acknowledged and accounted for in the consultation. Therefore, addressing CRC patients' beliefs and resolving treatment related psychological distress may be a crucial step in supporting adherence. In addition, an educational session at the outset of treatment and direction given in the clinic may not be sufficient to promote adherence. This research identified that individuals who were less well informed had difficulty recalling the purpose of the tablets, understanding how the medication works, or determining whether they were taking them for good reasons, which could unintentionally lead to sub-optimal adherence. As components of the adherence risk pre-screening tool, identifying patients with low health literacy, and addressing medication beliefs and preferences about drug information would enable more targeted patient education initiatives.

Healthcare providers should engage in constructive conversations with patients about information available online, as well as promote reliable resources for those seeking information using digital platforms. A patients' understanding and retention of treatment information has long been considered a factor likely to influence adherence behaviour. However, little is known about how health information research using online sources influences patient's medication adherence to oral chemotherapy medications. A recent study to determine the impact of information source on chronic prescription medication adherence stated that long-term adherence and overall beliefs about medication had a negative correlation with reliance on digital content for information regarding prescriptions (Arbuckle

et al. 2019). The authors also found that younger age groups, which are also the ones most at risk for non-adherence, prefer digital information sources. Thus, CRC patients should be educated on how to better utilise digital content for oral chemotherapy related information, as it may help with improving confidence and adherence to the medication. More research is also needed on the influence of digital platforms on medication adherence among CRC patients' taking oral chemotherapy agents.

Lastly, this study suggests that the MARS self-report tool is not suited for assessing adherence to oral chemotherapy agents in this patient population, and its limitations are detailed in *section 6.10*. For example, regarding the MARS item '*i forget to take it*', only 50% of participants who reported forgetting a dose in the interviews also indicated forgetting a dose in the MARS survey, implying the possibility of recollection bias and social desirability. Additionally, because all respondents answered identically for five of the MARS items, meaningful analysis to test the scales psychometric properties was not possible. It would be useful to conduct further research with a larger sample size to explore if there is variation in responses and to enable more robust statistical analysis examining the ability of the MARS items to discriminate across WIMD categories of deprivation. Changing the language descriptors for the MARS scale, such as the shortened version, i.e., MARS-5 (Chan et al. 2019), which asks respondents to select a number from 1 to 5, where 1 indicates strongly disagree and 5 indicates strongly agree, could be considered to obtain more variation in response. Furthermore, the MARS self-report scale does not provide information about the time of daily intake or make the distinction between daily intake and daily adherence, which would provide more accurate information, i.e., whether the patient is under or overusing the medication.

Therefore, future research should consider developing a reliable and validated measure for the CRC population taking oral chemotherapy medications to ensure that patients' adherence is accurately recorded.

6.10 Strengths and Limitations

This study used an exploratory case study approach to triangulate the embedded units of analysis in order to provide an in-depth understanding of the factors influencing oral chemotherapy medication adherence in South Wales. The findings generated from the two sources of evidence complimented each other and contributed to an understanding of the intricate and often complex influences on medication adherence. The exploratory approach shed some light on aspects of social human thinking and behaviour, for example, the emotional vulnerability (low feelings) of participants during the first few cycles of treatment. A longitudinal study would be interesting to observe what happens over time; for example, do patients who had negative emotions or beliefs at the start of therapy continue to be at risk of non-adherence, or does this change with time. As the reasons for the primary findings in this study are inadequately described in the literature and may have therapeutic implications for the participants, these reports in real-life contexts open the way for further research into the phenomenon. This study is novel in that it explores the factors that influence oral chemotherapy medication adherence in different socioeconomic groups. Also, this study met its objective which was to provide an in-depth look at the complexity of the factors that influence adherence to oral chemotherapy medication among colorectal cancer patients, which may be transferable to other cohorts.

There were several limitations to this research that must be considered. Firstly, the sample lacked diversity (*see section 6.5*), as CRC patients were overwhelmingly white and averaged 65 years of age. Consequently, the findings are not representative of other ethnicities and younger age groups; future research should consider subgroup analysis using a broad patient population. It is possible that there are sociocultural issues and age gap differences impacting adherence, as they may encounter different challenges that are not identified in this study and that need to be taken into account. For example, younger patients may not prioritise or cope as well as older patients with their medication regimen (Wenzel et al. 1999; Verbrugghe et al. 2013a), or the impact of sociocultural influences on their perceptions of medication adherence (Megan C. Roberts et al. 2015), socioeconomic issues, or access to the healthcare system or providers.

The MARS measure used in this study was not previously validated for the CRC target population; as a result, it may be subject to measurement error, and only tentative conclusions can be drawn. This is because validated measurement tools have been tested and refined using the target population to establish good validity and reliability. Two items were removed from the MARS scale (*see section 3.5.3.1.2*), and the researcher accepts that this creates a new questionnaire that should be psychometrically tested for confidence in the results. The researcher considered re-factor analysing the MARS items to determine if the items in the new scale measured the same construct as in studies that used the original measure, but this was not possible because there was insufficient data variability to test the scales' psychometric properties. Therefore, this should be taken into consideration, and

caution should be exercised when interpreting the study findings. This may suggest that the MARS self-report tool is not suited for assessing adherence to oral chemotherapy agents in the CRC patient population. Thus, it would also be useful to conduct more work with a bigger sample size to demonstrate that the MARS questionnaire is a reliable and valid tool for assessing adherence in this patient population.

Furthermore, the readability of some MARS statements used in the self-report measure raised concerns about their usefulness for measuring patient adherence to the oral chemotherapy medication. The small number of participants (5.1%, n=3), who did not comply with the MARS statement, *"I only use my (*name of medicine*) when I need it"*, was highlighted as a limitation. Several participants asked for this item to be repeated, implying that the question's wording generated some difficulty. This was the first item on the questionnaire, so a misunderstanding of the item may have led to a choice error. Moreover, as the individuals were predominantly elderly, they had additional co-morbidities that impaired their mobility (dexterity), hand-eye coordination, and vision, all of which were documented during the pilot run. Even when provisions were made to print the surveys in large font sizes, participants felt more comfortable with the researcher reading the questions and recording the responses. It was feasible to put the participants at ease from the start by taking the time to discuss the research and read the information sheet and consent form aloud while providing them opportunities to engage and ask questions. The use of the think aloud method has implications for evaluating the psychometric features of self-report tools, because the cognitive process of responding to a question may be hampered by the inability of participants to understand or recall an answer. By using the first level of simple vocalisation

(Ericsson and Simon 1993), a survey question's meaning may be affected by a difficult phrase structure or unfamiliar terminology. Also, there is still the risk of recall bias and social desirability, i.e., the Hawthorne effect (Ruddy et al. 2009). However, in developing a new self-reported adherence measure, the think aloud method could be used to gain insight into problems with interpreting and understanding question items. The approach offers a unique perspective on how people complete questionnaires and the challenges they face.

Due to the lack of a gold standard approach for measuring medication adherence, it is advised that various methods be used to determine the level of agreement between these measures (Walter et al. 2014). This study made use of self-report methods, which have the benefit of being easily applied in clinical settings and placing minimal burden on participants. Previous literature has often used self-report tools, and this provides some reassurance that comparisons can be made between studies. Nevertheless, the interviews allowed the researcher to dig deeper into some of the survey responses by repeating statements made by the participants and comparing responses, such as instances when they forgot to take their oral chemotherapy medication.

The data was unable to identify other prescribed medications, such as those receiving combination therapy along with the oral chemotherapy agent. In addition, the researcher acknowledges that participants were receiving different treatments at different cycles of the illness journey (e.g., adjuvant-curative intent, palliative intent), which is likely to have affected their experiences (and thus adherence). In this study, 25.4% (n=15) of participants received single-agent treatment, while 74.6% (n=44) were prescribed two or more medications

(mean=3.2). During interviews, some individuals who received combination IV chemotherapy reported that the nursing personnel gave them additional counselling, which could potentially influence their adherence behaviour. It wasn't apparent whether these participants had tailored IV infusion sessions and/or medication counselling to address concerns about their oral chemotherapy treatment. Future research should collect full treatment regimens and compare those receiving combination therapy versus single agent treatment to determine whether there is a difference in side effect profiles and care management that impacts adherence to the oral chemotherapy medicines. Also, whether patients were receiving treatment with different intent (such as, adjuvant treatment vs palliative intent) to determine whether this influences their medication-taking behaviour and, consequently, adherence to oral chemotherapy treatment.

6.11 Dissemination Plan

Dissemination will take various formats and include distribution to key stakeholders and publication of articles with reputable target journals:

- The plans are to publish the main findings of the study titled *“Exploring the physical, emotional, and physical factors that influence adherence to oral chemotherapy treatment in the home”*. This paper will present findings of two embedded units of analysis that explored the influences on adherence and medication-taking behaviour among CRC patients in South Wales. Target journals for publication include: *The British Medical Journal (BMJ) Open, European Journal of Oncology Nursing, Cancer Chemotherapy and pharmacology, Journal of Oncology Pharmacy Practise, Support Cancer Care.*

- A summary of the findings will be sent through the post or by email to the 38 participants who had requested them. The summary will include the number of participants who completed the questionnaires and interviews and the main findings from the interviews.
- Local dissemination summarising the findings will be sent to the Velindre University NHS Trust health board research and development team and to contacts made during the study period who have asked for feedback such as staff members of the colorectal specialist multidisciplinary team (including medical consultants), chief pharmacist, and the outpatient nurse manager.
- A short report with an overview of the study findings will be provided to the funders and Health and Care Research Wales Portfolio. The thesis will also be made available on the Cardiff University repository.
- Presentations will be organised to provide an overview of the main findings to postgraduate students and lecturers at the university. Opportunities will be taken to display posters and oral presentations at national and virtual international conferences. Conference suggestions include Healthcare Sciences Postgraduate Research Symposium, The International Society of Medication Adherence (ESPACOMP) annual conference, British Oncology Pharmacy Association (BOPA) Annual Symposium.

6.12 Reflexivity

Previous chapters (section 1.2 and section 3.5.5.5) have addressed my positionality as a pharmacist and researcher. Since then, I have reflected on my journey and taken notes of my thoughts and feelings, which include both positive and challenging aspects of the research project. Some of these points will be discussed below.

I applied for NHS ethics approvals through the Integrated Research Application System (IRAS). Initially, I had not accounted for the time required to apply for ethical approval in my research plan due to the specific requirements of the IRAS application. It seemed rational for studies that posed a risk to participants to offer detailed information on the study's purpose and the forms of analysis. I sent individual emails to each of the medical consultants, the chief pharmacist, and the outpatient nurse manager to obtain permission to conduct the study. I was asked to present the research project to senior pharmacy colleagues at a management meeting. Moreover, two consultants requested separate meetings to discuss the recruitment process and its impact on the clinic's operations. I feel that obtaining these permissions prior to applying for ethical approval really helped with establishing rapport with the multidisciplinary CRC teams during data collection. At the outpatient clinic, the welcoming nature of the medical staff was common, and they all took the time to assist me in any way possible, and the consultants were personable.

There were challenges to obtaining permissions, notably when it came to audio recording medical consultations with participants. The idea was for the researcher to gain insight into how CRC patients and clinicians discuss medication adherence issues in their natural environment. The medical consultants were concerned about the sensitivity and confidentiality of their medical conversations with patients. Therefore, they gave permission to observe and take notes at each session. Although this was an adjustment to my research protocol, I did not foresee any issues at this stage. However, due to the fast-paced conversations and intricacy of the topics discussed during the consultations, I found it difficult

to take verbatim notes, which the quality of the research was dependent on. Later, it was decided together with my supervisors to use the observational sessions to create a patient profile. This would make it easier to talk about medication adherence issues during the interviews.

During the data collection process, the number of participants recruited at each session was determined by the list of patients scheduled for morning clinic appointments. Increasingly complicated patient cases meant there was occasionally a backlog of patients in the waiting area, reducing the likelihood of recruiting new participants. Also, several clinics had medical and nursing students observing medical staff, making it difficult to communicate with clinicians about their patient lists. Nonetheless, CRC patients were keen to support the study and acknowledged it was an important topic. A summary of the research findings will be sent through the post or by email to 38 participants who had requested them.

I realise, with reflection, that conducting the interviews was a learning experience for me. I was conscious of how my line of inquiry aligned with the research objectives in order to collect rich information that accurately portrayed the realities of the participants. As previously noted regarding my positionality and its implications (see *section 3.5.5.5*), I continually reflected on how my own actions, values, and perceptions impacted the research as participants constructed meanings that portrayed the true state of the phenomenon under study. My previous experience as a pharmacist conducting medication use reviews was useful when following up a line of inquiry within the context of this research. It was helpful to be able to redirect the conversation back to the topic at hand, as I noticed that participants

tended to drift away from it. I thought that it was key to listen carefully and ask open-ended questions to find out important information.

My initial thoughts were that I realised how complex the issues were with the factors influencing medication adherence to oral chemotherapy agents. Participants who were most averse to taking the oral chemotherapy or who were non-adherent had either experienced the treatment's side effects themselves or knew someone who had. As my experience with interviews developed, I was able to overlay additional topics discussed with participants on top of previously gathered information, such as the information sources used to learn about the oral chemotherapy drug. However, when familiarising myself with the interviews, I found it difficult to separate myself from the data, since much of the information I listened to and read in the transcripts appeared to be familiar on the surface. I needed to be clear about information that was based on my own interpretation of the data. It was also important to obtain a new perspective on the data in order to differentiate the differences and increase credibility. One interview transcript was independently coded by my supervisor, an academic and qualified nurse. This was a strength because it helped in the development of the analytical framework, and it was also nice to learn that the majority of codes were comparable so that differences could be analysed.

Using my professional judgement to best place codes that did not fall into a specific category or theme was one of the challenges. Also, I found the process of sifting through all the textual codes and refining the analytical framework to be immersive. The process required continuous refinement and supervisory team meetings until no new codes emerged from the data. As I analysed the interview data, I was aware of the importance of paying close attention

to the research question and how it informed my thinking. In addition to ensuring that the data collected reflected the patient's perspective on the factors influencing adherence to oral chemotherapy medicines.

During the writing process, several thoughts regarding the relevance of the findings for clinical practice, healthcare providers, and research emerged. There were also several examples of some deep findings relating to the participants' meaning making. However, at times, I struggled to find the right balance between the findings relating to participants' meaning making and my role as a researcher in interpreting the results in a manner that best served the research goals. Member checking with the supervisory team, a re-evaluation of the methodological approach, and positionality were all important in achieving this balance to ensure that I was concise and that the findings spoke to the focus of the research. Above all, this study has led me to acknowledge that, whilst previous research has focused on oral chemotherapy medication adherence, there are multi-faceted reasons for non-adherence, and a holistic approach is required to support CRC patients' medication-taking behaviour.

6.13 Conclusion

This study contributes to the growing body of knowledge about medication adherence, a significant subject with long-term implications for patients, families, and healthcare systems. *The Quality Statement for Cancer (2021)*, an investment from the Welsh Government as part of its commitment to address the needs of people affected by cancer, highlights the importance of person-centred care. The study has shown how colorectal cancer patients taking oral chemotherapy medications experience complex challenges that influence their

adherence decisions. The findings of this study suggest a potential trend in the disparity of medication adherence scores across different sociodemographic groups, emphasising the importance of addressing socioeconomic inequalities for health equity. The exploratory nature of this study, combined with the small sample size and preliminary analysis, warrants caution in interpreting the results as a definitive conclusion. However, they do provide valuable insights and suggest the need for more extensive research to validate and expand upon these initial observations.

Adherence decisions are heavily influenced by symptom management, and patients should be educated on how to recognise potential side effects early and in a timely manner, taking into account patient preferences. Patients should also be informed about practical methods for remembering to take their medication doses. When patients do not take their medication as prescribed, they risk improper dosing and increased treatment toxicity. This necessitates routine follow-up support that is targeted to patients' educational, and lifestyle needs, as well as authenticated digital information sources to better equip patients with medication adherence. A holistic approach provided by multidisciplinary care teams, including community support groups, may be more effective in helping patients cope with taking medication regularly, particularly for patients with risk factors for lower adherence. These include CRC patients from lower socioeconomic groups with signs of psychological distress.

More people are living longer with cancer as oral chemotherapy treatments have improved over the last decade, and the focus has shifted to solutions beyond the medication. The findings of this study can be used as a starting point for developing educational training programs that are customised to meet the needs of CRC patients. Given that all patients

receive cancer care, it is hoped that better understanding patient views of factors that influence adherence behaviours will inform future educational tools to improve healthcare services and practice, potentially leading to better clinical outcomes.

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Appendix 1: Ethical Approval



Professor Jane Hopkinson
School of Healthcare Sciences
College of Biomedical and Life Sciences
Cardiff University, 12th Floor Eastgate House, 35-43
Newport Road, Cardiff
CF24 0AB

Email: hra.approval@nhs.net
HCRW_approvals@wales.nhs.uk

11 July 2019

Dear Professor Hopkinson

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title: What factors (including patient beliefs about medication) influence adherence to oral chemotherapy treatment among colorectal cancer patients in socially deprived locations, as compared to more affluent areas in the South East Wales region.

IRAS project ID: 260079
Protocol number: SPON 1746-19
REC reference: 19/NS/0121
Sponsor: Cardiff University

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to [obtain local agreement](#) in accordance with their procedures.

What are my notification responsibilities during the study?

The attached document "*After HRA Approval – guidance for sponsors and investigators*" gives detailed guidance on reporting expectations for studies with HRA and HCRW Approval, including:

- Registration of Research
- Notifying amendments
- Notifying the end of the study

The [HRA website](#) also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **260079**. Please quote this on all correspondence.

Yours sincerely,
Gurmel Bhachu

Email: HCRW.approvals@wales.nhs.uk

Copy to: *Mrs Helen Falconer*

Appendix 2: Project Sponsor



Research and
Innovation Services

Gwasanaethau Ymchwil
ac Arloesi

Cardiff University

McKenzie House, 7th Floor
30-36 Newport Road, Cardiff
CF24 0DE, Wales, UK
Tel +44(0)29 2087 5834
www.cardiff.ac.uk

Prifysgol Caerdydd

Ty McKenzie, 7th Llawr
30-36 Heol Casnewydd, Caerdydd
CF24 0DE, Cymru, DU
Ffôn +44(0)29 2087 5834
www.caerdydd.ac.uk

5th June 2019

Professor Jane Hopkinson
School of Healthcare Sciences
Cardiff University
13th Floor, Eastgate House
35-43 Newport Road
Cardiff
CF24 0AB

Dear Professor Hopkinson,

Adherence and Patient Beliefs to Oral Chemotherapy treatment in colorectal cancer patients

I understand that you are acting as Chief Investigator and Academic Supervisor for the above PhD project to be conducted by Abdiraheem Ali.

I confirm that Cardiff University agrees in principle to act as Sponsor for the above project, as required by the UK Policy Framework for Health and Social Care Research.

Scientific Review

I can also confirm that Scientific Review has been obtained from: the Knowledge Economy Skills Scholarship (KESS2) funding programme.

Insurance

The necessary insurance provisions will be in place prior to the project commencement. Cardiff University is insured with UMAL. Copies of the insurance certificate are attached to this letter.

Approvals

On completion of your IRAS form (required for NHS REC and HRA/HCRW/NHS R&D permission), you will be required to obtain signature from the Research Governance team for the 'Declaration by the Sponsor Representative'. Please note that you are also required to provide the Organisation Information Document and Schedule of Events to the Research Governance team for review prior to submission to HRA/HCRW.

Please then submit the project to the following bodies for approval:

- an NHS Research Ethics Committee;
- Health & Care Research Wales (HCRW)- to arrange HRA/HCRW Approval for Welsh NHS sites.

The University is considered to have accepted Sponsorship when Research and Innovation Services has received evidence of the above approvals. **Responsibility for providing the Local Information Pack to NHS organisations is delegated from the Sponsor to the Chief Investigator (or their appropriate delegate). Once an NHS organisation has confirmed capacity and capability, responsibility lies with the Chief Investigator (or their appropriate delegate) to follow an appropriate 'green light' procedure to open the study at that Site.**

Roles and Responsibilities

As Chief Investigator you have signed a Declaration with the Sponsor to confirm that you will adhere to the standard responsibilities as set out by the UK Policy Framework for Health and Social Care Research. In accordance with the University's Research Integrity & Governance Code of Practice, the Chief Investigator



Registered Charity, no. 1136855
Eiwsen Gofrestredig, rhif 1136855

is also responsible for ensuring that each research team member is qualified and experienced to fulfil their delegated roles including ensuring adequate supervision, support and training.

If your study is adopted onto Health & Care Research Wales Clinical Research Portfolio you are required to upload recruitment data onto the portfolio database.

Contracts

- The HRA/HCRW Organisation Information Document will act as the agreement between the sponsor and participating NHS organisations.

May I take this opportunity to remind you that, as Chief Investigator, you are required to:


- register clinical trials in a publicly accessible database before recruitment of the first participant and ensure that the information is kept up to date
- ensure you are familiar with your responsibilities under the UK Policy Framework for Health and Social Care Research;
- undertake the study in accordance with Cardiff University's Research Integrity & Governance Code of Practice (available on the Cardiff University Staff and Student Intranet) and the principles of Good Clinical Practice;
- ensure the research complies with the General Data Protection Regulation 2016/679;
- where the study involves human tissue, ensure the research complies with the Human Tissue Act and the Cardiff University Code of Practice for Research involving Human Tissue (available on the Cardiff University Staff and Student Intranet);
- inform Research and Innovation Services of any amendments to the protocol or study design, (including changes to start /end dates) and submit amendments to the relevant approval bodies;
- respond to correspondence from the REC, HRA/HCRW and NHS organisation R&D offices within the required timeframes;
- co-operate with any audit, monitoring visit or inspection of the project files or any requests from Research and Innovation Services for further information.

You should quote the following unique reference number in any correspondence relating to Sponsorship for the above project:

SPON 1746-19

This reference number should be quoted on all documentation associated with this project.

Yours sincerely



PP

Dr K J Pittard Davies
Head of Research Governance and Contracts
Direct line: +44 (0) 29208 79274
Email: resgov@cardiff.ac.uk

Cc Abdiraheem Ali; Professor Molly Courtenay

Appendix 3: Insurance Certificate



TO WHOM IT MAY CONCERN

2nd July 2018

Dear Sir/Madam

CARDIFF UNIVERSITY AND ALL ITS SUBSIDIARY COMPANIES

We confirm that the above Institution is a Member of U.M. Association Limited, and that the following covers are currently in place:

EMPLOYERS' LIABILITY

Certificate No.	Y016458QBE0118A/165
Period of Indemnity	1 st August 2018 to 31 st July 2019
Limit of Indemnity	£50,000,000 any one event unlimited in the aggregate
Includes	Indemnity to Principals
Cover provided by	QBE Insurance (Europe) Limited and Excess Insurers

PUBLIC AND PRODUCTS LIABILITY

Certificate of Entry No.	UM165/13
Period of Indemnity	1 st August 2018 to 31 st July 2019
Includes	Indemnity to Principals
Limit of Indemnity	£50,000,000 any one event and in the aggregate in respect of Products Liability and unlimited in the aggregate in respect of Public Liability
Cover provided by	U.M. Association Limited and Excess Cover Providers led by QBE Insurance (Europe) Limited

If you have any queries in respect of the above details, please do not hesitate to contact us.

Yours faithfully

Paul Cusition
For U.M. Association Limited

5 St Helen's Place, London EC3A 6AB | T: 020 7847 8670 | www.umal.co.uk

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Appendix 4: Velindre University NHS Trust Letter of Access for Research



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Wales
Ymddiriedolaeth GIG
Prifysgol Felindre
Velindre University
NHS Trust



Velindre University NHS Trust
Headquarters
Pencadlys Ymddiriedolaeth GIG Prifysgol
Felindre

2 Charnwood Court
Heol Billingsley
Parc Nantgarw
Cardiff
CF15 7QZ

Tel/Ffon : (029) 2061588
www.velindre-tr.wales.nhs.uk

Correspondence to: Mrs Sarah Townsend, Research and Development Manager, Velindre University NHS Trust, Research & Development Office, Velindre Cancer Centre, Velindre Road, Whitchurch, Cardiff, CF14 2TL
Email: Sarah.Townsend@wales.nhs.uk
Tel: 029 20 615888 ext: 4670

Mr Abdiraheem Ali
School of Healthcare Sciences,
Cardiff University
12th Floor Eastgate House
35-43 Newport Road, Cardiff
NP20 0AB

12th July 2019

Dear Abdi,

Letter of access for research

In accepting this letter, Velindre University NHS Trust confirms your right of access to conduct research through the organisation for the purpose and on the terms and conditions set out below. This right of access commences on 12th July 2019 and ends on 12th July 2021 unless terminated earlier in accordance with the clauses below.

Velindre University NHS Trust is/are satisfied that the research activities that you will undertake in the Trust are commensurate with the activities you undertake for your employer. Your employer is fully responsible for ensuring such checks as are necessary have been carried out. Your employer has confirmed in writing to this organisation that the necessary pre-engagement checks are in place in accordance with the role you plan to carry out in the Trust. Evidence of checks should be available on request to Velindre University NHS Trust.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from Velindre University NHS Trust. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

You are considered to be a legal visitor to the Velindre University NHS Trust premises. You are not entitled to any form of payment or access to other benefits provided to Trust

Mae'r Ymddiriedolaeth hon yn croeso i gyswrtu goglebiaeth yn y Gymraeg
The Trust welcomes correspondence in Welsh





Ymddiriedolaeth GIG
Prifysgol Felindre
Velindre University
NHS Trust



Velindre University NHS Trust
Headquarters
Pencadlys Ymddiriedolaeth GIG Prifysgol
Felindre

2 Charwood Court
Heol Billingsley
Parc Nantgarw
Cardiff
CF15 7QZ

Tel/Ffon : (029) 2061588
www.velindre-tr.wales.nhs.uk

employees and this letter does not give rise to any other relationship between you and Velindre University NHS Trust, in particular that of an employee.

While undertaking research through Velindre University NHS Trust, you will remain accountable to your employer Cardiff University but you are required to follow the reasonable instructions of your nominated managers Sue Hopkins and Diana Osman in in Velindre University NHS Trust or those given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by Velindre University NHS Trust in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Velindre University NHS Trust's policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Velindre University NHS Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Velindre University NHS Trust premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and Velindre University NHS Trust prior to commencing your research role at each site.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 2018. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

Velindre University NHS Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 2018. Any breach of the

Mae'r Ymddiriedolaeth hon yn ddiarwain gobeithoedd yn y Gymraeg
This Trust welcomes correspondence in Welsh





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Data Protection Act 2018 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. If provided, please also ensure that while on the premises you wear your ID badge at all times. Please note that Velindre University NHS Trust accepts no responsibility for damage to or loss of personal property.

This letter may be revoked and your right to attend Velindre University NHS Trust terminated at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the Trust or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or suitability to work with adults or children, or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the organisation that employs you through its normal procedures. You must also inform the nominated manager in Velindre University NHS Trust.

Yours sincerely

Sarah Townsend (Mrs.)
Research & Development Manager and Sponsor Representative

Mae'r Ymddiriedolaeth hon yn croeso i gyswrtu gŵelwedd yn y Gymraeg
This Trust welcomes correspondence in Welsh



Appendix 5: Consent Form



Patient Consent Form

Participant Identification Number:

Study Title: What factors (including patient beliefs about medication) influence adherence to oral chemotherapy treatment among colorectal cancer patients in socially deprived locations, as compared to more affluent areas in the South East Wales region?

Main Contact: Abdi Ali

	Please Initial Box	
I can confirm that I have read and understood the information sheet dated 08/07/19 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.		
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.		
I agree to the researcher attending and observing my medication review appointment with my clinician. I understand that this appointment will not be recorded but that the researcher may take notes during the appointment.	YES	NO
	<input type="checkbox"/>	<input type="checkbox"/>
I agree for the researcher to contact me to arrange a short interview about the study.	YES	NO
	<input type="checkbox"/>	<input type="checkbox"/>
I agree for the interview to be audio-recorded for the above study.	YES	NO
	<input type="checkbox"/>	<input type="checkbox"/>
I agree to the use of my word-for-word (verbatim) quotes in any publications about the research. I understand that no one will be able to identify me from my quotes.	YES	NO
	<input type="checkbox"/>	<input type="checkbox"/>
I understand that the researcher will have access to my		

IRAS: 200679

PATIENT CONSENT FORM - VERSION 2 08/07/2019

ONE COPY FOR THE PARTICIPANT. ONE COPY FOR THE RESEARCH SITE FILE

1

research data and give permission to access this information. I understand that all my data will be kept securely at Cardiff University for 15 years and will be made publicly available.	
I understand that all information collected will be kept confidential.	
I understand that individuals may look at relevant sections of my data collected during the study, from Cardiff University or from Velindre University NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I understand that my details will be provided to the Cardiff University Finance Team for the purpose of processing any travel expenses.	
I agree to take part in the above study	

Full Name:

Signature:

Date:

Name of Researcher	Signature	Date

Appendix 6: Patient Information Sheet

Funded by
tenovus
cancer care
gofal cancer

 **GIG**
CYMRU
NHS
WALLS | Ymddiriedolaeth GIG
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Velindre University
NHS Trust

kess
Knowledge Economy Skills
Innovation

CARDIFF
UNIVERSITY
PRIFYSGOL
CAERDYDD

Patient Information Sheet

Study Title: What factors (including patient beliefs about medication) influence adherence to oral chemotherapy treatment among colorectal cancer patients in socially deprived locations, as compared to more affluent areas in the South East Wales region.

Main Contact: Abdi Ali

My name is Abdi Ali, and I am a Postgraduate Research Student at Cardiff University. My key interest area is in understanding adherence to oral chemotherapy treatment.

You are being invited to take part in this research as you are currently taking oral chemotherapy medication. This information sheet will explain to you the purpose of the study, why you are being asked to take part and what the study involves. Before you consider taking part, it is important you take time to read the information below to understand why we are doing this research.

In order to make an informed decision about your choice on whether to participate, please feel free to discuss this with your family, friends or members of the healthcare team. Please also feel free to ask if there is anything that is not clear, and you would like more information. Contact telephone numbers and details of how to obtain further information on this study are provided at the end of this leaflet.

Thank you in advance for taking the time to read this information sheet.

What is the purpose of the study?

The purpose of this study is to understand how people taking chemotherapy medication, specifically the oral formulation such as tablets are managed in South East Wales. The factors that influence adherence or non-adherence to oral chemotherapy treatment have not been thoroughly investigated. We would like to understand your personal views on your chemotherapy medication and how you take these medicines. We would also like to know how satisfied you are with the medicine information you receive and how oral medication has impacted your day-to-day routine. The outcomes of this research will inform decisive interventions that are significant at improving adherence.

Why have I been invited to take part?

You have been invited to take part as you are taking chemotherapy medication and can help us improve our understanding on the different challenges people face with taking oral chemotherapy medication. To provide best care service it is important to know how the medicines are currently managed and the challenges that you may be experiencing. Your views will be important to help inform interventions that will provide better treatment outcomes for people on oral medication.

Do I have to take part in the study?

No. It is entirely your choice whether you would like to take part in any or all stages of the study. If you do agree to take part, we will ask you to sign a consent form. You can withdraw your consent at any time during the study and without the need for an explanation. However, we will need to keep any data you may have provided up until the point you

chose to leave the study and this data may be included in the final analysis. Withdrawing from the study will not affect the care and treatment you receive at Velindre or any other NHS hospital or service either now or in the future.

What will happen to me if I take part?

The research will take place in two phases as described below. If you do choose to take part in the study, you do not have to take part in all of the phases if you don't want to:

1. The first phase of the study will involve a two-part questionnaire. The aim of this questionnaire is to explore how people manage their oral chemotherapy treatment. It should take no longer than 20 minutes to complete. If you have signed the consent form and would like to complete the survey in your own time, please send the completed survey forms using the pre-paid envelope addressed to 12th Floor Eastgate House, Cardiff University.

After completing the questionnaire, some participants may be contacted by the researcher to arrange a suitable time for an interview and/or observation of their medication review appointment. Just like the questionnaire, you do not have to take part in either of these phases of the study if you do not want to.

2. The second phase of the study will be an observation of your medication review with your clinician to gain a better understanding of adherence influencing behaviours with taking chemotherapy tablets. This will involve the researcher sitting in the room during the appointment with your clinician or the oncology pharmacist and taking notes. The researcher is interested in observing the conversations you have with your clinician. You will not be required to do anything additional during your appointment and should continue the appointment as normal. The researcher will not record any details about your medical history, but will need to note details of your current illness and any treatment and medication you are receiving.

If you choose to complete the questionnaire you may also be invited to talk about your experiences in a short interview. The interview will either be face to face or can be undertaken over the telephone.

Where will the interview be held?

The interview will take place at a time and a place that is suitable for you. If you decide to take part in the study, the researcher will call to arrange the interview. Travel expenses will be reimbursed if you decide to travel to the Cardiff University campus for the interview. It will last no longer than 45-60 minutes and it will be audio recorded. The recordings will be securely stored at Cardiff University. The interview recording will then be typed up into a written record (transcript). The university approved transcription provider will be chosen from a list of providers that are available at data analysis. The Cardiff university process involves issuing an annual tender to establish a list of verified transcribers that can be used. All subsequent contracts will include confidentiality agreements and University standards. All personal data (any information that could identify you) will be removed from the transcript. With your permission we would like to use your 'word-for-word' (verbatim) quotes in the final publications and presentations, but we will ensure that no one will be able to identify you from your quotes.

Who is organising and funding the research?

Knowledge Economy Skills Scholarships (KESS2) and Tenovus Cancer Care fund the project.

Will my taking part in the study be kept confidential?

Absolutely. Throughout the course of the study, the confidentiality and privacy of participants will be respected. The researcher will take the utmost care to ensure that all records and conversations are kept confidentially. Only the staff at Velindre NHS Trust and the Cardiff University researchers will know that you are taking part in the study.

Each participant will be given a unique six-digit identification number to retain anonymity so that you cannot be identified and your privacy protected. No one will be able to identify you from the study results.

If unethical practises are observed however, or there is patient safety concerns such as breach of information containing patient identifiable details. This will be dealt with the utmost importance. In the scenario that there was a breach of information, the relevant patient and authorities will be informed as per the Velindre NHS Trust and Cardiff University policies.

What are the possible benefits of taking part in the study?

There are no specific benefits for research participants, however sharing your views will be for the wider benefit of future patients. The outcomes of this research will inform interventions for improving adherence. It will enhance the current research knowledge on oral chemotherapy treatment and inform future educational tools to support patient adherence to oral chemotherapy agents.

What will happen to information about me?

Cardiff University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means we are responsible for looking after your information and using it properly. Cardiff University will keep all research data for 15 years once the study is completed.

Your rights to access, change or move your information is limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we

will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about Cardiff University Data Protection policy and procedures by visiting the site below:

<https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection> or by contacting the University's Data Protection Officer: inforequest@cardiff.ac.uk

Velindre NHS Trust will approach you about the research in accordance with our instructions. With your permission, Velindre NHS Trust will pass these details to Cardiff University along with any information collected from you.

Cardiff University will use your name and contact information to contact you about the research and make sure that relevant information about the study is recorded for your care. Velindre NHS Trust and Cardiff University will oversee the quality of the study. Individuals from Cardiff University and regulatory organisations may look at your research records to check the accuracy of the research study. The only people in Cardiff University who will have access to information that identifies you will be those who are conducting or supervising the study; those who need to contact you about the research or audit the data collection process.

Cardiff University will keep personal identifiable information about you from this study for up to six months after the study has finished.

What steps will be taken if a participant, who has given informed consent, loses capacity to consent during the study?

The researcher will be guided by principles set out in the Mental Capacity Act 2005. In the scenario that a participant loses capacity during the study they will be withdrawn from the study. Identifiable data already collected with consent will be retained and used in the study. No further data will be collected or any other research procedures carried out in relation to the participant.

What if there is a problem?

If you have any concern about any aspect of the study, you should ask to speak to the research team who will do their best to answer your questions. Email Abdi at alia15@cardiff.ac.uk or call 07821437936. Alternatively you can contact the researchers' academic supervisors Professor Jane Hopkinson (tel: 02920688562 or email hopkinsonjb@cardiff.ac.uk) or Professor Molly Courtenay (tel: 02920688566 or email courtenaym@cardiff.ac.uk). If you remain unhappy and wish to complain formally, you can contact the Cardiff University School of Healthcare Science Research Governance Lead, Dr Kate Button by emailing buttonk@cardiff.ac.uk or contact: 02920 687734.

Who has reviewed the study?

Before any research goes ahead it has to be checked by the Research Ethics Committee. This is to ensure that the research is fair and is following set guidelines. The North of Scotland Research Ethics Committee (1) has reviewed this study.

What will happen to the results of the study?

The results of the study will be published as part of Abdi Ali's Cardiff University PhD thesis. The results will also be published in academic journals and may be presented at conferences and meetings. Only anonymised data will be included in any publications or presentations. This means that your name and other identifying details will not be included in any publicly-available results.

If you would like a summary of the study results at the end of the study, please let Abdi know.

Thank you for taking the time in reading this – please feel free to ask any questions

Appendix 7: Interview Topic Guide Sheet



GIG
CYMRU
NHS
WALES

Ymddiriedolaeth GIG
Prifysgol Felindre
Velindre University
NHS Trust



Participant Interview – Topic Guide

Participant Identification Number:

- Patient view on adherence decisions and influencing factors:
 - Social and economic
 - ✓ Social support network
 - Patient-related
 - ✓ Adherence
 - ✓ Self-management of medication
 - ✓ Knowledge of condition and medication
 - Therapy related
 - ✓ Patient counselling on medication use
 - Health system related
 - ✓ Information from healthcare providers
 - ✓ Clinical and social support system
 - Condition-related
 - ✓ Co-morbidities
- Patient knowledge and beliefs about oral chemotherapy medication:
 - Beliefs and perceptions about the medication
 - Expectations and concerns about the medication
 - Barriers and facilitators of medication adherence
- General beliefs about medication
- Side-effects of medication

Appendix 8: Questionnaire Survey



GIG
CYMRU
NHS
WALLES

Ymddiriedolaeth GIG
Prifysgol Felindre
Velindre University
NHS Trust



Participant Questionnaire Survey

Participant Identification Number:

Study Title: What factors (including patient beliefs about medication) influence adherence to oral chemotherapy treatment among colorectal cancer patients in socially deprived locations, as compared to more affluent areas in the South East Wales region?

Section A:

Medication Adherence Report Scale (MARS)

"Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines. For each statement, please tick the box which best applies to you"

How often do you use the following? Please focus **solely** on the oral chemotherapy medicine(s) used to treat your colorectal cancer.

Rated: 1 = Very Often, 2 = Often 3 = Sometimes, 4 = Rarely and 5 = Never

	Very Often	Often	Sometimes	Rarely	Never
I only use my (*Name of Medicine*) when I need it					
I decide to miss out a dose					
I try to avoid using it					
I forget to take it					
I alter the dose					
I stop taking it for a while					

I use it as a reserve, if my other treatment doesn't work					
I take it less than instructed					

Section B:

The Beliefs about Medicines Questionnaire (BMQ):

PART ONE: BMQ-Specific Necessity Scale:

Your views about oral chemotherapy medicine(s) prescribed for you:

"We would like to ask you about your personal views about oral medicine(s) prescribed for your colorectal cancer. These are statements other people have made about their medicines. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views."

Rated: 1 = strongly agree, 2 = agree, 3 = uncertain, 4 = disagree and 5 = strongly disagree

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
My health, at present, depends on my medicines					
Having to take medicines worries me					
My life would be impossible without my medicines					
Without my medicines I would be very ill					
I sometimes worry about long-term effects of my					

medicines					
My medicines are a mystery to me					
My health in the future will depend on my medicines					
My medicines disrupt my life					
I sometimes worry about becoming too dependent on my medicines					
My medicines protect me from becoming worse					

PART TWO: BMQ-General Scales:

Your views about medicines in general:

"We would like to ask you about your personal views about medicines in general. These are statements other people have made about medicines in general. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views."

Rated: 1 = strongly agree, 2 = agree, 3 = uncertain, 4 = disagree and 5 = strongly disagree

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
Doctors prescribe too many medicines					
People who take medicines should stop their treatment for a while every now and again					
Most medicines are addictive					

Natural remedies are safer than medicines					
Medicines do more harm than good					
All medicines are poisons					
Doctors place too much trust on medicines					
If doctors had more time with patients they would prescribe fewer medicines					

Section C:

Socio-Demographic and Health Related Survey:

Gender: Male Female

Age:

Ethnicity origin: Please specify your ethnicity

White <input type="checkbox"/>	Asian (other) <input type="checkbox"/>	Bangladeshi <input type="checkbox"/>	Black African <input type="checkbox"/>
Black British <input type="checkbox"/>	Black Caribbean <input type="checkbox"/>	Black (other) <input type="checkbox"/>	Chinese <input type="checkbox"/>
Hispanic or Latino <input type="checkbox"/>	Indian <input type="checkbox"/>	Pakistani <input type="checkbox"/>	Other (please specify): <input type="checkbox"/>

Marital Status: what is your marital status?

Single <input type="checkbox"/>	Married <input type="checkbox"/>	Widowed <input type="checkbox"/>	Divorced <input type="checkbox"/>
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Separated <input type="checkbox"/>			
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Education: What is the highest degree or level of school you have completed? *If you are currently enrolled, please state the highest received.*

1 or more GCSE's <input type="checkbox"/>	1 or more O Levels/ A-Levels <input type="checkbox"/>
Professional Diploma or equivalent <input type="checkbox"/>	Bachelor's degree <input type="checkbox"/>
Master's degree <input type="checkbox"/>	Doctorate/PhD <input type="checkbox"/>
No Qualifications <input type="checkbox"/>	Other (please specify): <input type="checkbox"/>

Employment status: are you currently?

Employed <input type="checkbox"/>	Self-employed <input type="checkbox"/>	Not in Work <input type="checkbox"/>	Student <input type="checkbox"/>
Retired <input type="checkbox"/>	Unable to Work <input type="checkbox"/>	Prefer not to say <input type="checkbox"/>	

Area or Location of Residence: which category describes your local authority?

Vale of Glamorgan <input type="checkbox"/>	Rhondda Cynon Taff <input type="checkbox"/>	Merthyr Tydfil <input type="checkbox"/>
Caerphilly <input type="checkbox"/>	Cardiff <input type="checkbox"/>	Newport <input type="checkbox"/>
Bleanau Gwent <input type="checkbox"/>	Torfaen <input type="checkbox"/>	Monmouthshire <input type="checkbox"/>
Bridgend <input type="checkbox"/>	Don't Know <input type="checkbox"/>	

How long have you lived in this area?

0-1 years <input type="checkbox"/>	1-2 years <input type="checkbox"/>	2-3 years <input type="checkbox"/>	3-4 years <input type="checkbox"/>	4+ years <input type="checkbox"/>
---------------------------------------	---------------------------------------	---------------------------------------	---------------------------------------	--------------------------------------

Which category describes your colorectal cancer condition?

Adenocarcinoma <input type="checkbox"/>	Gastrointestinal Stromal Tumours (GIST) <input type="checkbox"/>	Lymphoma <input type="checkbox"/>
Carcinoids <input type="checkbox"/>	Turcot Syndrome <input type="checkbox"/>	Peutz-Jeghers Syndrome (PJS) <input type="checkbox"/>
Familial Colorectal Cancer (FCC) <input type="checkbox"/>	Other, please state: <input type="checkbox"/>	Don't Know <input type="checkbox"/>

Which oral formulation(s) are you currently taking to treat your condition? Select all that apply to you:

Tablets <input type="checkbox"/>	Buccal or Sublingual tablets <input type="checkbox"/>	Capsules <input type="checkbox"/>	Liquid <input type="checkbox"/>
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How many prescribed medication(s) are you currently taking?

1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 or more <input type="checkbox"/>
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Which oral chemotherapy medication are you currently taking for your condition? Select all that apply to you:

Capecitabine (Xeloda®) <input type="checkbox"/>	Lonsurf® (Trifluridine + Tipiracil) <input type="checkbox"/>	Other (please state): <input type="checkbox"/>	Don't Know <input type="checkbox"/>
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Section D:

Please indicate whether you would be happy to be followed up with a short interview?

Yes No

If yes, please state below how you would prefer to be contacted:

Email:

Telephone/Mobile:

Please state whether you would like to receive a summary of the research findings?

Yes No

If yes, please provide details below to receive this information:

Email:

Address:

Thank you for taking the time to complete this questionnaire survey – please feel free to ask any questions.

Contact Information:

Abdi Ali (Researcher): alia15@cardiff.ac.uk or call 07821437936

Appendix 9: Examples of Data Analysis Coding

Sample 1: Developing a working analytical framework

An initial analytical framework based on the WHO framework (WHO, 2003) was developed, as well as familiarisation with the transcript data. The researcher coded transcripts according to the initial analytical framework and left open codes for segments that did not fit the framework. Interesting segments of the text were underlined, and the transcripts were printed with large margins. Particular attention was given to the research question and how it informed my critical thinking. The process of refining, applying, and refining the analytical framework was repeated until no new codes were produced.

1	until, I think it was last week that I forgot, I accidentally forgot an evening dose, or morning	Abdiraheem Ali forgetfulness
2	dose but I thought well that is fine because I'll just take it then, it was just be another half a	Abdiraheem Ali acceptance of failure
3	day or day really, But that is the only dose that I have kind of forgotten about.	Abdiraheem Ali forgetfulness - dosage
4	A: You know, as humans like you said you do have to remember to be taking these doses and	Abdiraheem Ali
5	you've been taking them over a span of a year. In that time, what would say would be the	
6	challenges, like forgetfulness what were your challenges?	
7	P000034: I think it's fine when you're at home, it's possibly when you're out and about, Like I	Abdiraheem Ali challenges to forgetfulness
8	recall, we sort of went shopping over Christmas one time, and we went late in the afternoon	Abdiraheem Ali dosing regimen
9	and we decided to eat out. We were kind of ready for food by 5 o'clock and I said to my	Abdiraheem Ali
10	husband, "Ideally I can't eat for another hour at least" you know, kind of thing. In order to be	Abdiraheem Ali dosing regimen - routine break
11	within that 9-hour range really, minimum of a 9 hour gap between breakfast and evening	Abdiraheem Ali challenges to adherence - dosing regimen - routine break
12	meal, it's fine in the house, it's when your outside or you got other meals planned as well.	Abdiraheem Ali
13	A: Is that when you break your routine?	
14	P000034: I suppose it would be breaking a routine, yes. By the time we got to this restaurant	Abdiraheem Ali breaking routine
15	and we ordered then, it was fine anyway I didn't eat until 6.30pm so that was fine to take the	
16	tablets by then. I think as well going to eat for lunch with the girls this Friday for someone's	Abdiraheem Ali
17	birthday and we're going up in the afternoon. If I have lunch in the afternoon I don't always	Abdiraheem Ali break in routine
18	fancy tea so that becomes a bit of a challenge, and I need to have something fairly substantial	
19	in order to take the medication, But it's fine you know, couple of yoghurts and some fruits	
20	and that's fine.	
21	A: Yeah, so do you self-manage your medication?	
22	P000034: Yes absolutely.	

Sample 2: Applying the analytical framework

By applying the final analytical framework, the researcher carefully reviewed each transcript, highlighting meaningful passages of text, and selecting and attaching an appropriate code. DocTools was used to extract the textual data and corresponding codes into a separate Word document in a tabular format. The data extracted included the page number, the textual data to which the code relates, the original codes, and the author. Below is a sample from a transcript illustrating the extraction in a tabular format.

Comments extracted from: [https://cf-my.sharepoint.com/personal/alia15_cardiff_ac_uk/Documents/Data Analysis/Transcribed Interviews/P000058/AA Patient Interview Transcription P000058.docx](https://cf-my.sharepoint.com/personal/alia15_cardiff_ac_uk/Documents/Data%20Analysis/Transcribed%20Interviews/P000058/AA%20Patient%20Interview%20Transcription%20P000058.docx)
 Created by: Abdiraheem Ali
 Creation date: July 22, 2020

Page	Comment scope	Comment text	Author	Date
	You know, to stop me thinking these stupid things I was thinking.			
11	I seen my doctor and she said, "yes, we'll do it for a week and that should help you then to come back down". So I've come back down now and I feel fine.	increase in dose – depression (low feelings)	Abdiraheem Ali	08-Jun-2020
11	I've only got to ask, pick the phone up and they are always here	family support	Abdiraheem Ali	08-Jun-2020
12	I take medication for my chest, for my COPD. And I take a tablet for my prostate	Pre-existing condition	Abdiraheem Ali	08-Jun-2020
12	They told me I got cancer and, I went down like a rocket then, downhill	low feelings	Abdiraheem Ali	08-Jun-2020
13	he said, "otherwise we'll get you through this".	reassurance – doctor	Abdiraheem Ali	08-Jun-2020
13	The other doctor and that lady Ms Williams fair play pull it on in my head to me like I said, what is going to happen what it is going to be like	reassurance – trust	Abdiraheem Ali	08-Jun-2020
13	that's it I'm going that way and I'm staying that way. And I have	determination	Abdiraheem Ali	08-Jun-2020
13	I didn't know what is was going to do me	Uncertainty with treatment	Abdiraheem Ali	08-Jun-2020

Sample 3: Charting data into the framework matrix

The extracted data was charted into a spreadsheet matrix using Microsoft Excel, and a separate tab was created for each theme. The data was effective in identifying interesting codes that were mapped into the framework matrix. As shown below, a section from theme one (patient-related factors) that showed the framework matrix had one row for each participant and one column for each code with verbatim quotes that were grouped by categories. The researcher dug deeper into the data analysis, looking for emerging patterns that could explain the phenomenon beyond the individual participant reports.

Participants	Oral Chemotherapy - Dosing Regimen	Following Instructions	Routine	Adverse Effects of the Treatment	Side effects
P000004		"I go to the doctors and they explain everything to me about it. About what I got to take and what treatment I'm on and they explain it all to me down there"(pg.3), "What they tell me to do I would follow"(pg.3)			tiredness - "It affects your social life because you're so tired"(pg.2), "...feeling tired 24/7."(pg.8); Vomiting - "I would vomit for a day or maybe two after that treatment with the tablets"(pg.9); Infections - "I used to pick up an infection often...kept giving me infections I used to go in there every 6-7 weeks I used to end up back in hospital having treatment for infections."(pg.9)
P000006		"I was given the amount of tablets to take for the next two weeks which I stuck to rigidly."(pg.3), "I was doing as I was told"(pg.5)	"You know you got to take these things, so you get into a routine then."(pg.4)		
P000011					Hand-foot syndrome - "I told them I was feeling numbness in my fingertips."(pg.2); Taste (film-coating) - "...the main one for me is the taste. You lose your taste. Everything tastes bland and not particularly nice."(pg.7), "I am eating it's just disappointing when I do eat. It doesn't taste like how I expect it to"(pg.7) Tiredness (fatigue) - "...the fatigue after 4-5 days after treatment that's when I start to get tired."(pg.7)
P000012		12 hour interval - "say I woke at 9 o'clock in the morning I would take it 6 o'clock at night. I tried to get it in that habit if you know what I mean between 9 and 10 hours after the first one because otherwise you take it late at night "(pg.5)	"they've given you a routine to take it - you've got to have a routine!"(pg.13)		Hand-foot syndrome - "...the treatment has left me with numb hands and feet"(pg.2); Diarrhoea - "...it was making me quite ill like diarrhoea which was one of the worst things that was happening"(pg.2)
P000016		"I do adhere to as much as I can really. I do always follow like instructions that always say they have to be a certain time of the day, after food. I have always been religious time-wise"(pg.5), "I might take them a bit late sometime if I'm busy doing something"(pg.6)	"I am so religious on taking them...I think because of the regime because I'm so used to the times and you know like I say I get up and I have breakfast I have the tablets and that's the morning routine"(pg.6), "...it is a routine		Hand-foot syndrome - "The side effects of the capecitabine are very dry skin on the hands and the feet. It affects the nerve endings which in affect walking is...not really difficult but I can only walk so far"(pg.4), "...the main problem at the time as you say that affected me the most was my sore feet. Because they would be so sore, the skin is so dry and it gets cracked