

**Managing treatment and living with
chronic myeloid leukaemia**

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Abstract

Background

Chronic myeloid leukaemia (CML), a rare blood cancer, was transformed at the turn of this century from a disease with a poor prognosis to one with a chronic course as a result of a targeted therapy, imatinib; an oral tablet. Increasing prevalence has led to growing research interest in issues related to its chronicity such as quality of life and how patients manage their disease, including medication adherence. Little research exists examining the broad experience of patients living with CML within the context of their day to day lives and the health service providing treatment. In this thesis, I aimed to explore the patient and practitioner experience of living with and managing CML, and to produce findings which were relevant to clinical practice.

Methods

Qualitative semi-structured interviews were undertaken with a purposive sample of 17 CML patients and 13 practitioners from the same region in England. A thematic analysis of the interview data was carried out, and patient and practitioner findings compared.

Findings

Despite being perceived as a generally stable and uncomplicated disease, CML had a significant impact on patients' lives. Aspects of hospital care and social support systems had potential to buffer this. Patient disease knowledge varied and although a positive perspective was presented, anxieties remained. Practitioners worked with colleagues to support challenging treatment management, and had a broad understanding of the patient's context however lacked awareness of some aspects. A lack of standard approach to adherence was found and concerns regarding patient reporting of side-effects and non-adherence.

Conclusions

This thesis offers to raise practitioner, decision- and policy-maker awareness of the impacts of CML. Sharing care with primary or palliative care services may help to shift the perspective of CML from the hospital to a community setting, which considers the patient's broader context and encourages them to discuss anxieties and report concerns.

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Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references. The qualitative synthesis part of this thesis was published and copy of this is in appendix 4 (Hewison, A., Atkin, K., McCaughan, D., Smith, A., Smith, G., and Howell, D. 2020. Experiences of living with chronic myeloid leukaemia and adhering to tyrosine kinase inhibitors: A thematic synthesis of qualitative studies. *European Journal of Oncology Nursing*. April 45:101730, doi: 10.1016/j.ejon.2020.101730)

Chapter 1 Introduction

Haematological malignancies, or blood cancers, account for almost 9% of cancers in the UK (HMRN 2021^a) making them the fourth most common cancer in males and females across developed countries (Smith et al., 2010). Often defined as lymphoma, leukaemia and myeloma, based on the area of the body affected (lymph nodes, blood, bone respectively), classification has increasingly become more accurate as a result of developments in understanding of the cellular origins of different diseases, and their molecular and genetic characteristics (HMRN 2021^a; Smith et al., 2011; NICE, 2003). Consequently, inclusive of the latest revisions, the WHO International Classification of Diseases for Oncology (ICD-O3) used by practitioners internationally, now describes more than 100 different blood cancer types (Swerdlow et al., 2016; Jaffe et al., 2011).

Incidence, survival, disease and treatment pathways vary by disease sub-types, making this a heterogeneous cancer group (NICE 2016, Roman et al., 2016). Furthermore, ongoing patient needs as a result of the disease and/or its treatment are diverse, including psychological, practical and social concerns (Boyes et al., 2015; Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013). The increase in diagnostic accuracy has developed alongside novel, targeted therapies for cancer (NICE, 2003). One such therapy is used in the treatment of chronic myeloid leukaemia (CML). CML is a rare blood cancer and was a potentially fatal disease until the widespread use of a new targeted therapy; 'Gleevec' (generic name 'imatinib'; a tyrosine kinase inhibitor drug) at the turn of the 20th century (figure 1). This transformed the disease trajectory from acute to chronic, with the majority of patients now achieving normal life expectancy (Clark, 2020; Smith et al., 2014).

Figure 1: Front cover of Time magazine 28th May, 2001



In the UK, patients with CML are predominantly managed by haematology specialists within the NHS hospital outpatient system. Their response to tyrosine kinase inhibitor (TKI) therapy is monitored by molecular analysis of a blood sample taken every three to six months, carried out in an appropriate, accredited haematology laboratory (Hochhaus et al., 2020; Smith et al., 2020). Specialists review these samples and manage patients' treatment, for example by adjusting the dose or switching TKI type, to ensure they can tolerate the drug and their response meets treatment milestones set out in European guidance (Hochhaus et al., 2020). Patients are started on a TKI tablet soon after diagnosis, which is taken once or twice daily. This treatment is given to the patient to take within their home environment. Therefore, although the patient receives an appointment with a specialist doctor or nurse at least every three to six months, they essentially self-manage adherence to the treatment regime, within the context of their own lives on a daily basis. In addition to medication adherence, patients can face physical, emotional and practical consequences of the treatment and disease (Boyes et al., 2015; Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013). These effects have the potential to be experienced over a long period of time due to the chronicity of the disease and require decision making regarding their disease and health as part of their self-management.

The first cases of CML were thought to have been diagnosed in 1845 (Deininger, 2008), but it was not until the 1960s that CML was understood as a disease related to DNA, with the discovery of the faulty Philadelphia chromosome by Nowell and Hungerford (Nowell, 2007). Ground-breaking work by Janet Rowley in the 1970s identified the genetic translocation involved in this chromosome (Rowley, 1973). Rowley's work led to a greater understanding of the CML disease process and ultimately the development of imatinib (Watts, 2014). Much research effort has gone into the development of new, similar targeted tyrosine kinase inhibitor (TKI) drugs in order to improve the depth of treatment response (Baccarani, Efficace and Rosti, 2014), and recent developments have shown some patients can safely stop their medication (Saussele et al., 2018; Clark et al., 2017; Etienne et al., 2016).

As a result of increasing prevalence, research interest has now grown in exploring issues related to the long term impact of CML such as symptom burden, quality of life (QOL) and medication adherence (Zulbaran-Rojas et al., 2018; Efficace et al., 2014^a; Noens et al., 2014; Williams et al., 2013; Gater et al., 2012; Efficace et al., 2012^a). Much of this has been concerned with measuring different aspects of patient reported quality of life and identifying predictors of adherence to tyrosine kinase inhibitor (TKI) medication (targeted therapy of which imatinib/gleevec was the first used in CML). Some qualitative work also exists examining the patient experience of CML which often has a focus on adherence. This research is important in understanding the disease in the context of the patient's life and their own behaviour and perspective, which is of particular

relevance in CML; a disease where treatment is taken on a daily and long term basis by the patient at home. It may be of interest to practitioners who seek to understand why, despite the availability of a successful treatment, patients may struggle with treatment and may not reach optimum disease outcomes. My aim in this thesis is to investigate the experience of living with and being treated for CML from a broad perspective which considers the patient's context. I also aim to examine this alongside practitioner experiences of caring for patients with CML, in order to provide evidence which is of relevance to clinical practice.

The introductory chapter will begin by providing a background on CML; its incidence and survival. A discussion follows regarding the CML disease process, its treatment, and treatment response. Understanding the disease and its successful treatment is important as it emphasises that if treatment is taken, most patients with CML can live a lifespan similar to that of the general population (Baccarani et al., 2013) meaning the impact of CML may be experienced over a lifetime. The chapter then explores the impact of treatment on quality of life, the relationship of adherence to disease response and the role of self-management, key aspects of living with and managing the disease over a lifetime. It is this chronicity which means that CML becomes part of daily life and therefore, becomes impacted by the patient's broader context in which they experience their illness. Such contextual influences include social support, employment and relationship with their practitioner. In this thesis I propose that this individual patient context can influence how the disease is self-managed. Finally in this introductory chapter, I describe the aims and structure of the thesis.

1.1 Incidence, survival and prevalence

Reports on CML incidence from European countries appear to have increased in recent years, yet there is less evidence from countries outside the USA and Europe. Often incidence rates are taken from national cancer registries. The surveillance, epidemiology and end results (SEER) program covering many areas in the USA, reported an incidence rate of 1.7 per 100,000 population from 1975-2005 (SEER, 2020). Findings from the Surveillance of Rare Cancers in Europe (RARECARE) project using 89 European cancer registries found a crude incidence rate of 1.2 per 100,000 population (Visser et al., 2012). Other smaller reports from European registries report age standardised incidence of between 0.8 – 2 per 100,000 population, variably covering the years of 1980 until 2012 (Di Felice et al., 2018; Beinortas et al., 2016; Lauseker et al., 2016; Thielen et al., 2016; Penot et al., 2015). Rohrbacher and Hasford (2009) suggest variations in incidence rates could be explained by differences in ethnicity and geography, although there is little evidence for this.

Changes over time to the World Health Organisation (WHO) International Classification of Diseases for Oncology (ICD-O) definition of CML could also account for differences in incidence. In addition, haematological cancers can pose difficulties to cancer registries in accurately obtaining and coding cases (Smith et al., 2010). One of the largest population based cohort studies is the Haematological Malignancy Research Network (HMRN) in the UK. This is a registry of all patients in the Yorkshire and Humberside region diagnosed with haematological malignancies, and reflects the UK's population for age, sex and deprivation (Smith et al., 2011). Through its collaboration with NHS practitioners and a specialist diagnostic laboratory, HMRN has overcome problems common to most other registries, and is able to produce accurate and comprehensive data. HMRN data reports an annual age and sex specific incidence rate of 1.1 per 100,000 population, with CML comprising 1.6% of all haematological cancers (HMRN 2021^b).

The median age at CML diagnosis is reported to be between 56 and 58 years and incidence increases with older age (Brunner et al., 2013; Pulte et al., 2013; Smith et al., 2011; Rohrbacher and Hasford, 2009). Incidence is also higher in men than women, a ratio of 1.4 in HMRN data. Little difference in incidence has been found in terms of ethnic origin and geographical area (Hehlmann, Hochhaus and Baccarani, 2007). In the UK, socioeconomic status has not been shown to effect CML incidence nationally and within the HMRN area (NCIN 2014; Smith et al., 2011). This differs from some other cancers such as lung and melanoma where there is a strong association with social class (Shack et al., 2008).

Survival rates for patients with CML have improved significantly since the introduction of oral TKI drugs (including imatinib), having increased by nearly 50% since the late 1990s (Brunner et al., 2013; NCIN, 2013). European registries report a five year relative survival rate following the introduction of TKIs of between 55 - 88.7% (Di Felice et al., 2018; Beinortas et al., 2016; Gunnarsson et al., 2016; Lauseker et al., 2016; Thielen et al., 2016; Penot et al., 2015). In the UK, HMRN data report this figure to be 89.1% (HMRN 2021^b) and in the USA, 70.4% (SEER 2020). Differences in survival rates can partly be explained by the years examined by the studies, reflecting the growing use of imatinib. Lower survival rates may be due to delayed access to TKIs and lower TKI penetrance in some European countries (Beinortas et al., 2016; Kurtovic-Kozaric et al., 2016) and the personal cost of drugs and monitoring to patients in the USA (Abboud et al., 2013); all issues which may also be reflected in low income countries not examined in the literature. Experts point to the lower survival rate in the US and argue that the cost of imatinib is "unsustainable" and must be reduced to increase its uptake and therefore improve response and survival (Abboud et al., 2013). Novartis's patent for imatinib expired in 2016 in Europe and the USA, which has the potential to significantly change this situation, yet there may be other costs to patients such as disease monitoring. In the UK, where TKI

drugs and related care/monitoring are provided free of charge to the patient through the NHS, a study using HMRN data has shown a significant difference in the five year relative survival between those living in the most affluent areas compared to those in the least affluent, the least affluent having significantly worse survival (Smith et al., 2014). These findings imply that a patients' social context may influence their outcome, with the authors suggesting that poorer adherence could be a contributory factor.

Five year relative survival for patients with CML has been estimated to be higher for women than men, although this is not always statistically significant and underlying reasons appear unknown (Brunner et al., 2013; Pulte et al., 2013; Björkholm et al., 2011). However, more recent UK data shows very little difference between males and females in terms of survival (Smith et al., 2014). Age has also been shown to be related to survival; those in younger age groups having a better five year relative survival (Beinortas et al., 2016; Brunner et al., 2013; Pulte et al., 2013). Data from other studies however, suggests relative survival rates in older age groups is improving and nearing clinical trial estimates (Smith et al., 2014; Björkholm et al., 2011), reflecting work carried out demonstrating that imatinib is equally effective in all age groups (Gugliotta et al., 2011).

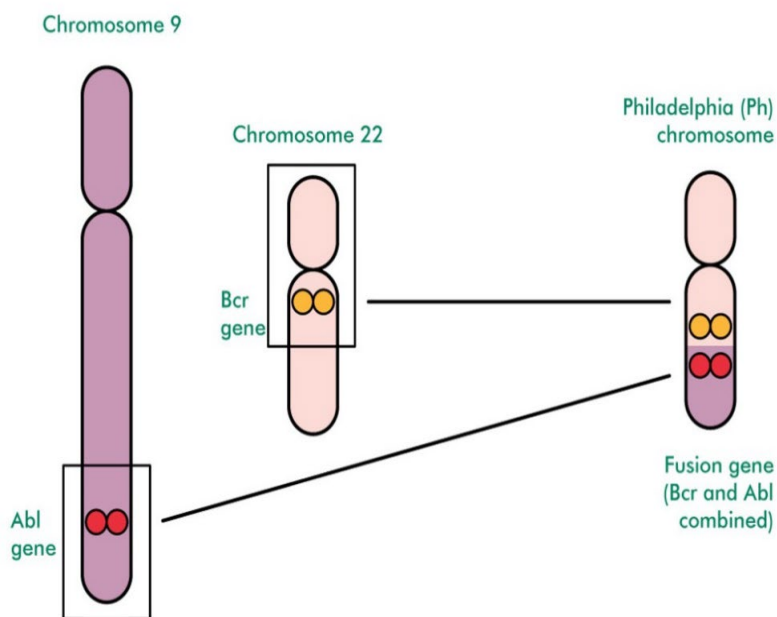
Survival in the UK has been reported to have improved since the advent of second generation TKI drugs developed since imatinib (Francis et al., 2013). Some survival outcomes may be significantly worse in those taking imatinib as first line treatment, compared to those taking a second generation TKI according to previous clinical trial data (Jain et al., 2015). However, studies comparing clinical trial data have not shown any significant difference in overall survival between imatinib and second generation TKIs (Jain et al., 2015; Sasaki et al., 2015), and UK and USA guidance suggest there is no evidence to support worse survival for those prescribed imatinib as first line treatment (Smith et al., 2020), or for any of the TKIs, despite second generation TKIs having a quicker and deeper response (Radich et al., 2018).

Better survival has led to increased prevalence of CML. Prevalence in Sweden was found to have tripled between 1985 and 2012 (Gunnarsson et al., 2016) and in Germany prevalence is estimated increase from 9000 people in 2012, to 20,000 by 2040-2050 (Lauseker et al., 2016). UK data approximates 5456 people overall living with CML who were diagnosed within the last 10 years, with an estimated prevalence of 8.3/100,000 people (HMRN 2021^b). As authors highlight, this increase has significant implications for healthcare systems and health economics (Gunnarsson et al., 2016). Living with CML over prolonged time-periods also has personal implications for patients' quality of life and requires long-term disease self-management, as discussed later in this chapter to justify the focus of the thesis. Next, I explain the disease process and its treatment. This enables an understanding of treatment response and its importance in the lifelong nature of CML.

1.2 The CML disease process

CML is a disease of stem cells which originate in the bone marrow and produce blood cells (Frazer, Irvine and McMullin, 2007). In more than 95% of cases these diseased cells carry a defective gene (Howard and Hamilton, 2013). In most people with CML the defective gene is found on an abnormal chromosome called the Philadelphia chromosome (Nowell and Hungerford, 1960). This chromosome is made when a part of the normally occurring chromosomes 9 and 22 break off and swap to join the other chromosome, which is referred to as translocation (see figure 2) (Howard and Hamilton, 2013). On chromosome 9 the part which breaks off contains the *ABL* gene and this joins to the point of chromosome 22 which contains the *BCR* gene; where they meet is described as the break point and makes a new gene on the Philadelphia chromosome called *BCR-ABL₁*.

Figure 2: The Philadelphia chromosome



The *BCR-ABL₁* gene produces a protein called tyrosine kinase but in a defective form. Normally tyrosine kinase sends messages to cells to increase cell production, and can also instruct cell production to stop (Frazer, Irvine and McMullin, 2007; Hehlmann, Hochhaus and Baccarani, 2007). However, defective tyrosine kinase produced by the *BCR-ABL₁* gene is unable to regulate cell production and cell death normally, and the bone marrow becomes crowded with the abnormal white blood cells containing the Philadelphia chromosome. This also means that other cells are unable to function normally.

The cause of gene translocation in the development of CML has not been identified (Hehlmann, Hochhaus and Baccarani, 2007). However, work carried out studying atomic bomb survivors has shown a clear link between previous radiation exposure and increased CML risk (Preston et al., 1994; Ichimaru et al., 1991). A meta-analysis of cohort studies also found an increased risk of CML with occupational exposure to benzene (Vlaanderen et al., 2011). Increased risk in patients with HIV and Crohn's disease has also been reported but may be coincidental (Patel et al., 2012; Makarem et al., 2005). In addition, increased risk of CML has been reported in patients following solid organ transplant, although larger cohort studies are needed to confirm this finding (Dhanarajan et al., 2014). Finally, some studies suggest an increased risk of developing CML in those who smoke or are obese (Musselman et al., 2013; Strom et al., 2009).

There are three disease phases described in CML; chronic phase (CP), accelerated phase (AP) and blastic phase (BP) (Baccarani et al., 2013). Most patients, estimated to be 85% (Cortes 2004), are diagnosed when they are in the chronic phase and common symptoms at presentation include fatigue, pain, anaemia, weight loss and enlarged spleen (Howell et al., 2013; Brown and Cutler 2012; Navas et al., 2010), however some may be asymptomatic (CRUK, 2021). In the accelerated and blastic phases symptoms become more severe and treatment is changed and/or intensified (Baccarani et al., 2013). This thesis examined only those in the chronic phase.

1.3 Treatment for CML

Initially, treatment for CML consisted of radiotherapy, first used in the early 20th century (Baccarani et al., 2006; Goldman, 2003). By the 1960s the chemotherapy drug busulfan (Goldman, 2003) became widely used and later hydroxyurea, the first drug to improve survival from the disease (Baccarani et al., 2006). Five-year survival rates for patients treated with these drugs were 32% and 44% respectively (Hehlmann et al., 1993). However, allogenic stem cell transplant was the first treatment to offer a potential cure and started being used in eligible patients in the 1980s (Baccarani and Pane, 2014; Goldman, 2003; Silver et al., 1999). Around the same time, interferon alpha, a biological treatment which stimulates the immune system to suppress the Philadelphia chromosome, was introduced as treatment for CML (Talpez et al., 1986). Later it was used in combination with the chemotherapy drug Ara-C, and seen as the best treatment for those not eligible for stem cell transplant (O'Brien et al., 2012). Whilst interferon alpha improved survival rates, with up to 53% 9-10 year survival (Baccarani et al., 2003), it caused considerable adverse effects (Cortes and Kantarjian, 2012). Likewise, although allogenic stem cell transplant is still the only curative treatment for CML, it can only be used in patients who are fit enough (Cortes and

Kantarjian, 2012) and carries with it a risk of mortality and a significant risk of morbidity, particularly graft versus host disease (Baccarani et al., 2013).

Undoubtedly, the introduction of the TKI drug imatinib at the beginning of this millennium (Druker et al., 2001) has produced the largest treatment impact, and had an extraordinary effect on survival for patients with CML (Baccarani and Pane, 2014; O'Brien et al., 2012; Druker et al., 2006; Goldman, 2003). Indeed, it is held up as an exemplar for a future shift in the treatment of other cancers away from chemotherapy and towards targeted treatment (Baccarani and Pane, 2014; Goldman, 2003). The aim of CML treatment can now be for a "100% survival and normal quality of life" (Baccarani et al., 2013) and more recently a "treatment free remission" (Hochhaus et al., 2020). International clinical guidelines now recommend imatinib and newer 'second and third generation' TKI drugs including nilotinib and dasatinib, as treatment options for chronic phase CML (Hochhaus et al., 2020; Smith et al., 2020; Radich et al., 2018).

1.3.1 Treatment response

TKI drugs work by inhibiting the abnormal tyrosine kinase protein produced by the BCR-ABL gene (O'Brien et al., 2012; Deininger, 2008) and are taken in tablet form by the patient continuously on a daily or twice daily basis. Response to TKIs has been referred to by Baccarani et al (2013), in the European LeukaemiaNet recommendations for the management of CML 2013, as "the most important prognostic factor". Response to CML treatment is described in three major UK (British Society for Haematology/BSH), European (European LeukaemiaNet/ELN) and US (National Comprehensive Cancer Network/NCCN) treatment guidelines as: haematological response, cytogenetic response and molecular response (Hochhaus et al., 2020; Smith et al., 2020; Radich et al., 2018). Haematological response is a measure of blood counts, blasts (immature, abnormal white blood cells) in the blood and signs/symptoms of splenic disease (O'Brien et al., 2012; Baccarani et al., 2009). Cytogenetic response is a measure of Philadelphia chromosomes present during cell division (O'Brien et al., 2012; Baccarani et al., 2009). However, it is molecular monitoring which more strongly predicts outcome and forms the basis of judging if a patient meets "milestones" in terms of their disease response over time (Hochhaus et al., 2020; Smith et al., 2020). Molecular response is a measure of BCR-ABL messenger RNA (mRNA) (O'Brien et al., 2012; Baccarani et al., 2009) which replicates the instructions carried on the *BCR-ABL₁* gene and carries this outside the nucleus of the cell to use the tyrosine kinase protein to instruct cells to reproduce abnormally (CML Support, 2014).

The specialised test used to monitor *BCR-ABL₁* level is the quantitative reverse transcription polymerase chain reaction (QRT-PCR) test and is described as the best way to measure response to treatment (Baccarani et al., 2009). Molecular monitoring must be carried out by specialist

laboratories and blood samples for this are taken at specific timepoints, so that haematologists can judge if the patient meets milestones defined in international guidance at intervals of 3, 6 and 12 months following the start of therapy (Hochhaus et al., 2020; Smith et al., 2020) . If the patient does not meet these milestones the haematologist needs to decide whether treatment is to be continued or changed, to avoid a progression of disease, with the ultimate goal being in a stable major molecular response (MMR) (Hochhaus et al., 2020; Smith et al., 2020; Radich et al., 2018). Such decisions on “second and third line” treatment can become complex due to individual factors including adherence, drug tolerance and co-morbidity, and the safety profiles of the various TKIs now available for haematologists to prescribe (Hochhaus et al., 2020).

1.3.2 Choice of TKI drug

Imatinib soon became the first line drug of choice for CML, and has few contra-indications and no life-threatening side-effects (Hochhaus et al., 2020). However, as a result of resistance to imatinib in some patients, further “second” and “third” generation TKIs were developed. Dasatinib, nilotinib, bosutinib and ponatinib are now available to be prescribed in the UK by NHS specialists. Current guidance is clear on when haematologists need to consider a switch of TKI. Haematologists can be guided in their choice of second or third generation TKI by the presence of particular imatinib resistance mutations, however these are rare (Hehlmann, 2020) and although clinical trials have shown the efficacy of all the second and third generation drugs against imatinib, they have not been compared with each other within a trial. Furthermore, although each drug may produce a quicker, deeper response than imatinib, they all carry a different side effect profile, including some life-threatening complications such as cardiovascular events secondary to nilotinib (Hehlmann, 2020; Hochhaus et al., 2020; Smith et al., 2020).

The increased potency of second and third generation TKIs meant that these were considered as first line treatments, however their significant side effect profile led guidance to advise imatinib as first line treatment for most patients in the UK (Smith et al., 2020). Therefore, in the absence of a particular mutation causing resistance, and any clinical trial evidence comparing second generation TKIs, the decision regarding switching medication is complex, involving assessing individual patient risk depending on co-morbidity, cardiovascular parameters and tolerance of drugs (Smith et al., 2020). The possibility of safely discontinuing TKIs now adds further complexity to the choice of drug. Large clinical trial results have indicated that patients with a sustained deep molecular response can discontinue their TKI and current guidance indicates how haematologists can manage this (Hochhaus et al., 2020; Smith et al., 2020; Radich et al., 2018). This may also influence TKI choice, in that a second or third generation drug may be considered as first line treatment in those wishing to

discontinue sooner, for example younger women who wish to become pregnant, and therefore require a quicker, deeper response (Smith et al., 2020).

Finally, all three sets of international guidance (Hochhaus et al., 2020; Smith et al., 2020; Radich et al., 2018) detail the side effect profile of each drug including imatinib, which despite having less contraindications still carries a series of side-effects. The ELN guidance highlights research showing a relationship between TKI tolerance and quality of life, recognising the impact this could have over a lifetime of taking the drugs, and leading the authors to recommend further research in this area (Hochhaus et al., 2020). The NCCN guidance also suggests that the presence of side-effects may impact on adherence to medication, and advises that practitioners provide patient education about this issue and frequently monitor side-effects (Radich et al., 2018). The three sets of guidelines emphasise the importance of checking adherence to TKIs when response is not meeting milestones, or considering a change of TKI (Hochhaus et al., 2020; Smith et al., 2020; Radich et al., 2018). Overall, it seems there is evidence in these guidelines that practitioners dealing with complex treatment decisions and monitoring need also to consider issues related to quality of life and adherence.

1.4 Quality of Life

Although imatinib, and now other second and third generation TKIs, have clearly had an unprecedented impact on survival, a consequence of this increased prevalence is that people living with CML experience the disease and its treatment over a lifetime, as previously discussed. The chronicity of CML and its treatment effects has implications for quality of life (QOL) and this has led researchers to investigate the issue (Baccarani, Efficace and Rosti, 2014; Efficace et al., 2011). This is an important starting point for this thesis. CML can significantly change aspects of daily life including leisure and family time (Buzaglo et al., 2017; Yanamandra et al., 2017; Jönsson et al., 2012). Patients with CML have been found to report worse physical health related QOL than matched controls, and describe problems including fatigue, depression and anxiety, and worse overall symptom burden (Phillips et al., 2013; Efficace et al., 2011). Side-effects described by clinical trials as 'low grade' may have a considerable burden and impact on QOL when lived with on a daily basis over a lifetime (Efficace and Cannella, 2016; Flynn and Atallah, 2016; Baccarani, Efficace and Rosti, 2014; Efficace et al., 2012^a). Furthermore, poorer QOL has been associated with worse medication adherence (Sacha et al., 2017; Unnikrishnan et al., 2016; Almeida et al., 2013; Noens et al., 2009). The qualitative experience of how CML impacts on quality of life, however, is less well explored, and particularly with respect to how people give meaning to, and manage their illness, relative to their social context. Furthermore, practitioners' qualitative experience of managing quality of life issues alongside clinical decisions is unknown.

1.5 Medication compliance, adherence and concordance

As CML is now considered a chronic cancer with long-term survival, discussions about adherence have become especially relevant, and are now raised in international guidance, as mentioned previously (section 1.3.2 choice of TKI drug). Non-adherence to medication can limit its safety and clinically proven effectiveness (Holmes, Hughes, Morrison, 2014; Nieuwlaat et al., 2014). Non-adherence is common in many disorders across the world (Holmes, Hughes, Morrison, 2014) and the WHO have estimated that adherence is around 50% amongst developed countries (Sabate et al., 2003). It is often described as intentional or unintentional (Easthall and Barnett, 2017; Lehane and McCarthy, 2007). Intentional non-adherence implies a decision made by the patient not to adhere (Lehane and McCarthy, 2007). This can be for a variety of reasons, and is related to the individual's beliefs and motivations, for example they may lack of confidence in the efficacy of medication or decide not to adhere due to the impact of the medication on their daily life (NICE, 2009).

Unintentional non-adherence, however, suggests a more passive patient role where they are prevented from fully adhering due to a more practical problem, such as forgetfulness, poor understanding or physical impairment (Cross et al 2020; Easthall and Barnett, 2017; Lehane and McCarthy, 2007). Theoretical models of adherence can aid our understanding of non-adherent behaviour and intentional non-adherence in particular has been studied using such models (Lehane and McCarthy 2007). They also provide a basis for designing adherence interventions to support the patient. Two recent reviews found the use of theoretical models could be predictive of adherence (Holmes, Hughes, Morrison, 2014) and interventions based on theory were found to produce more effective medication adherence outcomes (Conn et al., 2016).

Leventhal and Cameron (1987) categorised theoretical models for understanding adherence as: biomedical, communication, behavioural, cognitive and self-regulatory. The biomedical model understands illness as a specific pathology of part of the body (Bradbury, 2009) which can be fixed using technical solutions such as medication (Munro et al 2007). However, this model disregards those individual behaviours and thought processes, and also external factors, impacting on intentional and unintentional non-adherence (Amico et al., 2017). The theory of communication, which believes that effective patient and practitioner communication optimises adherence, and behavioural theory which focusses on learning about adherence behaviour, tend to disregard the patient's social context, in which they negotiate the use of medication. While communication and behavioural approaches do have value, it is argued that they cannot operate in isolation (Munro et al 2007). Cognitive and self-regulatory models, often stemming from health psychology, offer more in terms of understanding adherence behaviour (Amico et al., 2017), with the cognitive health belief model, theory of reasoned action and theory of planned behaviour being common in theory led

adherence interventions (Holmes, Hughes, Morrison, 2014). These are concerned with the effects of perceptions, self-efficacy, attitudes, social norms and beliefs on adherence behaviour (Amico et al., 2017; Munro et al., 2007). Elements of interventions using these approaches include ensuring an awareness of the disease and treatment, and examining the individual's motivation to adhere (Amico et al., 2017).

The theoretical models of adherence described here vary in how they incorporate an understanding of the patient's social context, some perceiving this as how it is incorporated into individual beliefs (Amico et al., 2017). However, the model of adherence produced by the WHO incorporates many aspects of the models outlined here, offering an ecological understanding adherence, which includes not only the influence of individual beliefs and behaviours, but also the impact of local and structural contextual factors. The WHO model describes five "interacting dimensions"; patient related factors, therapy related factors, condition related factors, socioeconomic factors and health system related factors (Sabate et al., 2003). Patient related factors describe an individual's beliefs, attitudes, perceptions and knowledge towards their illness and medication. Therapy related factors address the actual medication, such as dose, frequency and side-effects, whereas condition related factors describe the 'demands' of the illness, including symptoms and co-morbidity. Healthcare system factors refer to systems such as those to obtain medication and issues affecting practitioners, and includes limited time and resources. Finally, the document describes socioeconomic factors' as including: social support networks, family dysfunction and transport costs. These dimensions include features of all the models described and therefore the WHO model has been chosen as a basis to understand adherence in this thesis, also reflecting the broad research question and consequent literature review.

The term 'adherence' is commonly used in CML literature, but other terms exist to describe this. Patient 'compliance' became an area of concern in medicine in the 1970s as a result of the growing number of people living with chronic disease and taking long-term medication (Nettleton 2013). The definition of compliance at this time, commonly referred to, is:

"The extent to which the patient's behaviour matches the prescriber's recommendations" (Haynes et al., 1979, cited by Horne)

However, this description has been criticised for implying that in order to reach optimal compliance, the patient does not play an active role in decisions they make about their medication behaviour and merely follows doctors' orders (Horne et al., 2005). It suggests the patient is to blame if they do not take their medication (Nettleton 2013). The term adherence was developed in response to this criticism and infers a more equitable relationship between the doctor and patient as the definition

accepts the patient's right to decide whether to take their medication, or not. This reflects the aim of modern medicine, to move away from 'doctor-centred' towards 'patient-centred' care (Nettleton 2013). Adherence is the term preferred by the World Health Organisation (Sebate et al., 2003), defined as follows:

“...the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.” (Sebate et al., 2003)

The term concordance was developed more recently and adds to the definition of adherence by suggesting that patients not only come to an agreement with their doctor but are comfortable about that agreement (Marinker and Shaw, 2003). Concordance is described as an approach which is concentrates on:

“the consultation process, in which doctor and patient agree therapeutic decisions that incorporate their respective views, to a wider concept which stretches from prescribing communication to patient support in medicine taking.” (Horne et al., 2005)

Concordance suggests that an awareness of the patient's perceptions of about their illness is necessary to understand their beliefs about their medication and that support should be available to negotiate how patients take their medication (Marinker and Shaw, 2003). This requires active participation by the patient which may be difficult for those used to a relationship of compliance with health care professionals (Eatock and Baker, 2007). Both adherence and concordance definitions reflect elements of the theoretical models of medication adherence described earlier, in that they acknowledge the role of an individual's perceptions, attitudes and beliefs regarding their medication. These definitions suggest not only a more active role by the patient, but also the practitioner. Little qualitative work exists exploring these roles and the patient practitioner relationship.

The three terms compliance, adherence and concordance are often used synonymously although they describe medication taking differently (Marinker and Shaw, 2003). NICE use the term adherence in their most recent guidance; “Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence” (NICE 2009). This guidance stresses the idea that the patient is not to blame if they do not take their medication and recommends a negotiative approach where the patient is supported to make an informed decision, barriers to medication taking are identified, and their beliefs and motivations are explored (NICE 2009). This seems similar

to the description of concordance, and perhaps demonstrates how the three terms may come to be used interchangeably. Much of the research into CML and medication taking uses the term adherence, and therefore practitioners are likely to be most familiar with this term. For this reason it seems appropriate to use the term adherence in this study.

1.5.1 Adherence to TKI treatment

Adherence is an important aspect of self-management, particularly as CML has now generally become a chronic, longstanding condition. Several studies have shown a link between lack of adherence to imatinib and poorer response (Almeida et al., 2013; Ganesan et al., 2011; Marin et al., 2010; Noens et al., 2009). Although a major molecular response is the main aim of TKI treatment (Hochhaus et al., 2020), Marin et al (2010) found that when adherence to imatinib was $\leq 90\%$, no complete molecular responses were seen, and where it was $\leq 80\%$ there were no major molecular responses. The CML Support Group (CML Support, 2014), which is supported by clinical experts, estimates that 90% medication adherence roughly equates to missing just three doses per month. However, a review of TKI adherence literature concluded that this 'forgiveness margin', i.e. the amount of medication that can be missed before it has a significant influence on clinical outcomes, is still 'unknown' (Noens et al., 2014). This may cause uncertainty for both patients and practitioners in estimating the risk of missing medication.

Reported imatinib adherence rates vary (Almeida et al., 2013; Ganesan et al., 2011; Marin et al., 2010; Noens et al., 2009), with one review reporting adherence of between 19-100% (Noens et al., 2009). Although this variation may be affected by differing study populations, type of TKI and measurement time-point, it may also be due to varied definitions and adherence measurement tools (Gater et al., 2012). Few studies describe an underlying theory which defines adherence to TKIs. This lack of definition extends to national policy.

1.5.2 Medication adherence policy and practice

International and national policy and guidance suggests a gap regarding medication adherence for patients with CML. In 2003, NICE produced their document "Improving outcomes in haematological cancers" (NICE 2003) which contained guidelines on the treatment on CML. Although imatinib was in relatively new at this time, it was accepted that treatment for CML and some other haematological cancers was predominantly self-administered oral medication. However, adherence to this medication is not mentioned as a complication of treatment in the NICE document, and the long-term follow-up of haematological cancers was measured only in terms of rate of relapse and secondary malignancy. Nevertheless, the authors do acknowledge that "follow-up may fulfil other functions than simply detection of recurrence or secondary malignancy" (NICE 2003).

As discussed earlier in this chapter, the WHO document “Adherence to long-term therapies” (Sabate et al., 2003) emphasises the effect of a combination of social, health care system, therapy, condition and patient related factors on medication adherence and relates these factors to nine different diseases, including cancer, although the chapter on cancer discusses adherence to palliative medication only. More recently, in 2010, the Department of Health in England launched the National Cancer Survivorship Initiative (NCSI), aimed at improving the care of people “living with and beyond cancer” through measures such as personalised care plans and encouraging self-management (Department of Health, Macmillan Cancer Support and NHS Improvement 2010). However, the document frequently refers to the care of patients ‘after treatment’ and during ‘remission’ which is not wholly applicable to patients with chronic stage CML on long term treatment, or indeed those with some other blood cancers, such as chronic lymphocytic leukaemia where management may solely involve active monitoring, highlighting a gap in the definition of survivorship for these diseases.

NICE “Medicines adherence” guidance (NICE 2009) recommends future research develops ‘effective, equitable interventions’ to encourage adherence, along with support for patients and staff to improve informed decision making. The National Co-ordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO) report “Concordance, adherence and compliance in medicine taking” concluded from their literature review that medication adherence in all diseases is associated with patient decisions about their requirement to take their tablets, and that research into how these decisions and perceptions are made can help shape future studies on developing effective interventions (Horne et al., 2005). This offers further justification for the aims of my thesis and the need to understand how people negotiate their experience. Self-management has become an increasingly important way of understanding this experience, and is considered in the following section.

1.6 Self-management in CML

Authors have questioned whether chronic cancer can be regarded as a chronic illness and CML in particular, with its lifetime course, long-term treatment, and need for adherence (Pizzoli et al., 2019; Berlinger and Gusamo, 2011). This would imply that chronic cancer, including CML, should be managed within the paradigm of chronic disease self-management, an approach which has become part of UK health service policy over the last two decades (Morden, Jinks and Ong, 2012). It is argued that self-management is crucial among cancer patients on long term treatment if their disease experience is to be enhanced (Maher, Velikova and Betteley, 2015).

Like CML, the prevalence of chronic illness is set to increase on a global scale resulting in increased pressure on healthcare resources (Beaglehole et al., 2005). This has contributed to an increased focus by health systems on the self-management of chronic illness (Ellis et al., 2017; Browning and Thomas, 2015). However, further to the need to manage health resources, it is argued self-management is an essential requirement for those living with a chronic illness who, despite frequent use of health services, spend the majority of their time managing alone or with their carers (NHS England, 2014). Furthermore, it promotes patient empowerment in decision making regarding their health, and the building of partnerships with health care providers (Grover and Joshi, 2014; NHS England, 2014; McCorkle et al., 2011). It recognises that care needs to be provided in the long term and replace an “acute prescriptive relationship” involved in the medical model (Grover and Joshi, 2014; McCorkle et al., 2011). Self-management has also been associated with healthier outcomes and less healthcare utilisation (Barker et al., 2017; Coleman et al., 2009; Lorig and Holman, 2003; Barlow et al., 2002; Lorig et al., 1999).

Barlow’s definition of self-management in relation to chronic disease is widely cited in the literature (van Hooft et al., 2017; Dwaarswaard et al., 2015; McCorkle et al., 2011) and is used as a basis for understanding the self-management of CML in this thesis, reflecting a holistic perception of the consequences of living with the disease:

“self-management refers to the individual’s ability to manage the symptoms, treatment, physical, and psychosocial consequences and lifestyle changes inherent in living with a chronic condition” (Barlow et al., 2002).

Lorig and Holman’s (2003) work at Stanford University, in the development of self-management programs (using their program described below), has been influential around the world (Ellis et al 2017). The authors describe the self-management of a chronic illness as a “lifetime task”, reflecting the course of CML (Lorig and Holman, 2003). They suggest that this self-management is made up of tasks described by Corbin and Strauss (1988): the medical management of illness, including adherence to a medication regime; the management of life roles, including adapting daily routine tasks; and emotional management, such as coming to terms with a new perspective as a result of the illness. The notion of self-management tasks will also be incorporated into this thesis in terms of understanding the CML experience beyond adherence to a medication regime.

UK health policy regarding self-management has been influenced by the work of Lorig et al (1999) and Wagner et al (1996). Wagner et al’s Chronic Care Model (CCM) emphasises how health systems need to re-organise their care of chronic disease patients through employing six elements, including

developing a disease specific database and the sharing of evidence based guidance with patients to promote joint decision making (Wagner, Austin and Von, 1996). It represents a move away from a reactive service to a more proactive patient centred approach with patients able to enhance their health related knowledge and decision making ability (Coulter, Roberts and Dixon, 2013; Coleman et al., 2009; Grover and Joshi, 2005). Bandura's (1978) self-efficacy theory is at the core of the Lorig et al's (1999) chronic disease self-management program (CDSMP), designed to increase confidence in self-management through education on action planning, decision making and management techniques (Lorig et al 1999). The CDSMP's teaching programme includes the use of cognitive techniques to manage symptoms, communicating with healthcare professionals and community resources, and coping with emotions including depression and fear. Both these models suggest self-management is influenced by the relationship patients have with healthcare professionals and that patients should be encouraged to work with health and community services. This has informed this thesis in terms of investigating CML also from the perspective of practitioners.

In England, the Expert Patient Programme (EPP) (Department of Health, 2001) followed by the Health and Social care integrated model of care (Department of Health 2006) were influenced by the CDSMP and CCM. NHS England's five year forward view (NHS England, 2014) highlighted an ongoing concern of caring for an increasing population of people with long term conditions, and pledged to "do more to support people to manage their own health" by investing significantly in evidence-based self-management programmes (NHSE, 2014). This led to the adoption of the House of Care model developed by the Kings Fund (Coulter, Roberts and Dixon, 2013) which identified four components in the management of long term conditions, recognising not only the need to empower individual patients to self-manage, but also the influence of commissioning, the organisation of clinical services and need for joint working between health and care sectors (NHSE, 2021). An awareness of the organisation of clinical services has influenced this thesis in recognising the importance of understanding practitioners' perspectives of CML care, in addition to the patient perspective. Self-management is also evident in national cancer care policy. The National Cancer Survivorship Initiative (NCSI) (Department of Health, 2010) promotes a change in health care to a focus on shared decision making and self-management, for those patients living "with or beyond cancer", which would appear to include those patients living with CML. This is echoed in the National Cancer Strategy (NHSE, 2015) which set out its aim to provide support for people to improve quality of life following treatment or to "achieve personal goals" if they will be living with cancer "for some time" (NHSE, 2015).

1.7 Chapter summary

CML is a rare cancer with growing prevalence as a result of the introduction of imatinib at the turn of this century, which led to the development of perceptions of CML as a chronic condition. Little work exists on incidence and survival outside Europe and the USA, and the figures discussed are largely based on European and American cancer registries. Although gender has some impact on incidence, other factors including age, socioeconomic status and ethnicity have little effect. Survival rates were found to vary globally possibly due to the timing of the studies, access to care and the cost of drugs to the patient. Work showing a socioeconomic divide in UK survival, where TKIs are provided free at the point of delivery, suggests other more contextual factors contribute to survival outcomes.

Most CML patients carry the faulty *BCR-ABL₁* gene on the Philadelphia chromosome, which produces the abnormal tyrosine kinase enzyme triggering the proliferation of abnormal white blood cells which cause CML. TKI drugs are a targeted, oral treatment which suppress the action of the *BCR-ABL₁* gene. Molecular monitoring of the level of *BCR-ABL₁* in the blood is a strong indicator of disease response and outcome, and is carried out by specialist laboratories. Haematologists must judge disease response against defined milestones. Now practicing in an era of several second and third generation TKI drugs in addition to imatinib, each with its own side-effects and contra-indications, and no clinical trial comparing these drugs as second line treatments, practitioners must make complex treatment decisions. TKIs may need to be modified or changed if response falls below target, and haematologists must consider patients tolerability, co-morbidity and the risk profile of each drug. Added to this complexity is the possibility of ultimately stopping TKI drugs once a stable and prolonged response is reached. Some CML practice guidance now suggests quality of life should also be considered in treatment management and makes reference to difficulties with adherence.

Studies show that quality of life for patients with CML is worse than that of the general population, and many areas of daily life can be impacted as the patient lives with CML in the long-term.

Adherence to TKIs is considered a strong predictor of molecular response, although levels of reported non-adherence vary amongst studies due to differences in adherence measurement and definition. Difficulty with adherence reminds us that CML is now a chronic condition, which individuals have to negotiate and self-manage. Self-management is a common approach used in UK health service policy and is understood in this thesis as a holistic term incorporating not only the medical management of disease, including medication adherence, but also coping with the emotional and practical consequences. This is in addition to an awareness that self-management is influenced by the relationship patients share with their practitioner. Adherence is the chosen term to describe patient medication behaviour in this thesis as it is the term used widely in related literature and by practitioners. UK policy lacks guidance on the long-term follow-up of CML patients,

with some calling for further research to investigate patient decision-making about medication management. The definition of adherence adopted by this thesis recognises both individual and contextual influences on adherence behaviour. This further supports the aims of this thesis which I will now describe in detail, along with the thesis structure.

1.8 Thesis aims and study design

Understandably, early research into CML took a biomedical approach that focused on developing effective treatments for this once fatal cancer. However, recent advances in treatment mean CML is now considered a long-term condition. This brings challenges in understanding the implications of living with the disease and its treatment in the long term, demanding a more social perspective and alternative research methods. Such investigation includes recognising the importance of adherence, albeit within the broader context of how people ascribe meaning to their illness.

As a consequence, the aims of this thesis are to:

- 1) Explore patient experiences of living with CML and managing treatment for CML
- 2) Examine how practitioners manage CML patient care
- 3) Provide evidence that is relevant to clinical practice which could be used to improve the care and support of CML patients

Qualitative research lends itself to understanding lived experiences as it takes a wide-ranging approach to investigating such phenomena. Little qualitative literature exists which takes a broad approach to investigating the CML experience. In-depth semi-structured interviews will therefore be used to examine experiences of patients with CML, as they live with their cancer and its treatment each day, and of practitioners (haematology consultants and nurse specialists) providing care. A qualitative synthesis of studies examining patient experiences of TKI treatment, and a literature review of factors related to adherence in CML patients will also be conducted. These will have independent value, and will also underpin topic guides for the in-depth interviews.

1.9 Structure of the thesis

Following this introductory chapter, a background literature review explores factors influencing adherence to TKIs, which is where much of the CML literature is situated. This aims to add context to the concept of adherence and, as discussed, is used to instruct the interview topic-guide. Next is a synthesis of the qualitative literature concerned with CML patient experiences. This offers further important context for the thesis, again to inform the topic-guide and provide a context in which to

later locate the interview findings. The methodology chapter then describes the research techniques employed and steps taken to ensure rigor, followed by three chapters presenting the analysis of findings from patient and practitioner interviews. Finally, the summary, discussion and conclusion chapters summarise my findings and explore the relationships between, and explanations behind them, in addition to considering how these findings relate to wider research and literature, and to policy and practice.

Chapter 2 Literature review: factors affecting adherence to TKIs in patients with CML

This chapter describes the large body of quantitative literature that explores factors affecting adherence to TKIs, with the aim of placing the CML experience of taking medication into a wider context. These contextual factors include socioeconomic features, patient and treatment characteristics, and issues concerned with the patient experience such as quality of life (QOL) and social support. Between 2011 and 2016, seven literature reviews were published on adherence to TKIs for CML (Alves et al., 2016; Almeida et al., 2014; Noens et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a, 2012^b; Breccia, Efficace and Alimena, 2011). To effectively sum up the literature, I decided to summarise these existing reviews, then conduct my own new and updated review of subsequent studies published since the most recent existing review. The next section describes findings of the previous seven literature reviews and is followed by my new literature review exploring to what extent more recent literature contributes to our understanding. This chapter introduces the topic of adherence, its measurement and impact on outcomes, and explores factors influencing it. The chapter provides valuable context for the thesis and informs later interviews with patients and practitioners.

2.1 Previous literature reviews of adherence to TKI medication for CML

2.1.1 Methodology

In order to locate existing literature reviews concerned with adherence to TKI medication, an initial search was performed using the Medline database. The search criteria is listed below. Search terms were based on the literature exploring different terms used for medication adherence described in the introduction (see section 1.5), in addition to database suggestions for alternative terms used for chronic myeloid leukaemia. This located four of the final seven reviews (Noens et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a; Breccia, Efficace and Alimena, 2011). At this point in the thesis, I was immersing myself in a range of literature concerned with CML, including adherence, and as a result of this search and using reference list searches, I located a further three reviews (Alves et al., 2016; Almeida et al., 2014; Jabbour et al., 2012^b). The search strategy, inclusion/exclusion criteria and Prisma flow diagram now follow:

Search strategy

Search terms

- Adherence *or* concordance *or* compliance

and

- Chronic myeloid leukaemia *or* Chronic myeloid leukemia *or* Leukaemia myelogenous chronic BCR-ABL positive

Database search limits:

- Include review articles only

Published studies searched using:

- MEDLINE database (1946 onwards) (Ovid)

Inclusion criteria

Participants

- A diagnosis of CML
- Patients are in the chronic phase of CML at the time of the study
- Treatment with TKIs
- Adults aged 18 and over
- Males and females

Phenomena of interest

- Factors associated with adherence to TKI drugs in CML patients

Context

- Any geographical location.

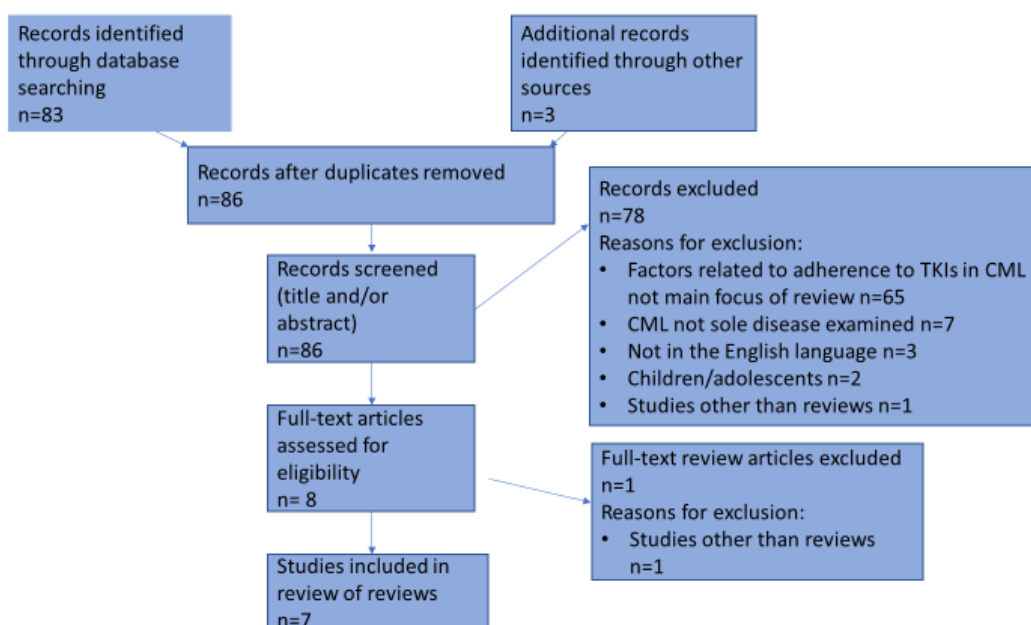
Types of studies

- Quantitative review studies describing factors associated with adherence to TKIs in patients with CML

Exclusion criteria

- Main aim is not the phenomena of interest
- Studies other than reviews
- CML not the sole disease examined
- Children/adolescents
- Not in the English language
- Qualitative review

Figure 3 Prisma flow diagram: literature reviews



Critical appraisal of literature reviews

In order to assess the quality of the seven existing reviews examined (Alves et al., 2016; Almeida et al., 2014; Noens et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a, 2012^b; Breccia, Efficace and Alimena, 2011), the CASP tool for critical appraisal of systematic reviews (CASP, 2021) was used as this is a well-known measure which can be applied to literature reviews (Aveyard, 2010), although some questions were not relevant (for example: “how precise are the results?”). The CASP tool begins with two screening questions; whether there is a defined review question and if the review

used the correct type of studies to answer this (CASP, 2021). Four of the reviews offered minimal, or no description of their methodology and did not meet these screening criteria (Almeida et al., 2014; Jabbour et al., 2012^a, 2012^b; Breccia, Efficace and Alimena, 2011); either having a much less defined aim/question (Almeida et al., 2014; Breccia, Efficace and Alimena, 2011) or not specifying this (Jabbour et al., 2012^a, 2012^b). It was therefore uncertain if these reviews chose the right papers for their review question as this was not specified. However, it was clear that well cited papers relating to CML adherence, for example Marin et al (2010), were included in all these reviews and they had interesting perspectives. For these reasons I decided to include them despite their lesser quality and failing the CASP tool screening questions.

The remaining three reviews (Alves et al., 2016; Noens et al., 2014; Gater et al., 2012) passed screening questions and were of higher quality in terms of reporting their methodology. Although there was no report of using unpublished studies, reference list searches or grey literature, all three used multiple search databases and two also searched conference abstracts. Multiple, relevant search terms were documented and inclusion/exclusion criteria clear. However, only one reported using a framework to critically appraise the included studies (Noens et al., 2014). The three reviews combined their findings into narrative under separate headings, with one also providing a conceptual model to demonstrate the complexity of adherence in CML (Gater et al., 2012). Reasons for heterogeneity between studies were considered within results and/or discussion sections and overall results were presented clearly. Non-adherence was found to be common (Alves et al., 2016; Gater et al., 2012), with varying rates (Alves et al., 2016) and reasons for non-adherence were described (Alves et al., 2016) with Gater et al's (2012) review highlighting the biopsychosocial nature of non-adherence. Gaps in the evidence were noted to be in terms of predictors of non-adherence (Alves et al., 2016), adherence measures and the classification of a gold standard measure of adherence (Noens et al; Gater et al., 2012), and defining adherence (Noens et al., 2014). Finally, in answer to the CASP question regarding applicability to a local population, the reviews did not set out to describe adherence in a specific population or setting therefore the question may not be wholly relevant, with reviews including all patients with CML on TKI drugs, covering a broad population.

2.1.2 Findings

Measurement and definition of adherence

The reviews showed a wide range of adherence rates, with Noens et al (2014) for example, reporting this as 19-100%. This could be due to factors affecting adherence in the populations included, different types of TKI drugs, or as Alves et al (2016) suggest, the time-point when adherence was measured (some studies show a higher level of adherence at treatment initiation). However, most

reviews explained that the variation could be due to the use of different adherence measurement tools and 'cut off' levels used to define adherence and non-adherence.

Medication possession ratio (MPR) was frequently used as an objective measure. This describes the total number of days a drug is available (i.e. the patient has collected their prescription), which is divided by the days the patient is eligible to receive their medication, often 365 (days of the year), and multiplied by 100 to obtain a percentage (Jabbour et al., 2012^b). Another objective measure reported in some studies was the medication events monitoring system (MEMS); an electronic device attached to the lid of the TKI pill bottle which records every time the bottle is opened (Breccia, Efficace and Alimena, 2011). Imatinib level in blood plasma (hOCT1) is a further objective measure which was used in some studies. Other objective methods included pill count and proportion of days covered (PDC: similar to MPR). Subjective measures of adherence included physician and patient reported outcomes, such as a visual analogue scale of adherence, qualitative patient interviews and questionnaires (Gater et al., 2012). Reviewers highlighted that each method of measurement is prone to bias. For example, MPR does not identify if patients have missed a dose or stopped due to instructions from their physician, only if their prescription had been collected on time (Breccia, Efficace and Alimena, 2011). In addition to the various measurements used, different studies also used different 'cut off' levels to define adherence. Marin et al (2010), for example, used MEMs and set non-adherence/adherence limits at <90%/≥90%, and (Wu et al., 2010^a) used MPR and defined <85% as low and ≥85% as a high adherence.

Overall, authors agreed there was no 'gold standard' measurement and 'cut off' level levels/definitions of adherence varied. Both Gater et al (2012) and Noens et al (2014) proposed more research to define adherence accurately, including "what it means to be adherent" (Gater et al., 2012). Importantly, Jabbour et al (2012^a) noted that despite these inconsistencies, it is clear that adherence is problematic for many CML patients, and in the absence of an ideal adherence measure, Breccia, Efficace and Alimena (2011), Gater et al (2012) and Noens et al (2014) advised the use of multiple methods in future studies.

Consequences of non-adherence

There is evidence that non-adherence impacts on disease response, notably a relationship between poorer adherence and poorer cytogenetic and molecular response. Two studies were frequently cited, and remain well cited in current literature: Noens et al (2009: the ADAGIO study) and Marin et al (2010). The ADAGIO study was one of few studies to use multiple methods to measure adherence and looked prospectively at patients taking imatinib across Belgium. Interestingly, the researchers chose not to use MEMS or MPR but a combination of interviews, self-reporting measures and pill

counts (Noens et al., 2009). Using pill counts the authors found that poorer adherence was significantly associated with a suboptimal cytogenetic response. Marin et al (2010) used MEMS to measure adherence in their well-known single centre UK study on patients established on imatinib, and found that MEMS and hOCT1 levels strongly predicted molecular response (Noens et al., 2009). Participants with adherence levels >90% were significantly more likely to achieve a major molecular response (MMR), while none of those <80% achieved MMR at 18 months (Marin et al., 2010). In a longer term follow up of these patients, using MEMS, Ibrahim et al (2011) found patients with poorer adherence were significantly more likely to lose their complete cytogenetic response (CCyR) at two years. Breccia, Efficace and Alimena (2011) and Jabbour et al (2012^a) cited two further studies showing that improved cytogenetic response was associated with greater adherence and imatinib dose (de Lavallade et al., 2008; Doti et al., 2007). Only one study across all seven reviews examined the relationship between survival and adherence (Ganesan et al., 2011), which showed that event free survival (EFS) for non-adherent patients was significantly worse than those with no dose interruptions, and achievement of CCyR was significantly worse (Ganesan et al., 2011). This perhaps explains the use of disease response as a strong surrogate measure for survival in research and practice, as advised by the European Leukaemia Network (ELN) guidance (Hochhaus et al., 2020; Baccarani et al., 2013).

Reviews also noted the consequence of improved adherence on lower healthcare costs, despite the high cost of the TKI drugs (Noens et al., 2014; Gater et al., 2012). Commonly cited studies were all USA based, of retrospective design and used MPR as their adherence measure (Wu et al., 2010^a; Darkow et al., 2007; Halpern, Barghout and Williams, 2007). Two of these found an association between better adherence and lower healthcare costs remained after controlling for other factors. However, these findings may not be generalisable to other countries due to them being USA based studies, where TKI treatment is not universally provided free of charge.

Factors affecting non-adherence

All seven reviews reported on predictors of adherence, with some studies cited more than others by the reviews; notably the ADAGIO (Noens et al., 2009) and Marin studies (Marin et al., 2010). Eliasson et al (2011) is also referred to by several reviewers, and although qualitative (examined in greater detail in chapter 3), is included here due to the importance of its contribution. A retrospective study of insurance claims in the USA (StCharles et al., 2009), was also frequently reported. In their conceptual model, Gater et al (2012) included a summary of factors affecting adherence, described under three useful headings: 'predisposing factors', 'patient interaction with the healthcare system' and 'patients direct experience'. As these headings offered a practical, logical framework, they were used to support the main findings from all seven reviews as follows.

Patient characteristics

Many review authors agreed that studies examining the predictive value of gender and age showed contradictory findings (Alves et al., 2016; Noens et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a, 2012^b). Decreased adherence was found to be more associated with younger age (Marin et al., 2010; StCharles et al., 2009), older age (Noens et al., 2014), or to have no association with age (Ganesan et al 2011). Similarly, there were conflicting findings regarding gender, with both male (Noens et al., 2014) and female genders (Darkow et al., 2007) related to higher non-adherence, or no relationship found (Ganesan et al., 2011; Marin et al., 2010).

Darkow et al (2007) and St Charles et al (2009) found non-adherence was significantly higher in those taking additional medication. However, Noens et al (2009) found that better adherence was associated with more concomitant medications taken. A similar variable; the presence of co-morbidities, was reported to be related to poorer adherence in two studies (Darkow et al., 2007; Noens et al., 2009).

Treatment characteristics

Most reviews identified various TKI drug related factors (Alves et al., 2016; Noens et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a, 2012^b; Breccia, Efficace and Alimena, 2011) as having an effect on adherence. Dose and time since treatment initiation was consistently related to adherence (Noens et al., 2014; Gater et al., 2012), a higher dose of imatinib was associated with poorer adherence (StCharles et al., 2009; Noens et al., 2009; Darkow et al., 2007), and adherence was observed to become worse over time (Noens et al., 2009; StCharles et al., 2009). Side-effects, or adverse events, were also associated with poorer adherence by several reviewers (Alves et al., 2016; Noens et al., 2014; Almeida et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a, 2012^b). Marin et al (2010) noted a relationship between side-effects and poorer adherence, and Eliasson et al's (2011) qualitative study showed adverse events to be a major reason for intentional non-adherence. Jabbour et al (2012^a) and Almeida et al (2014) discussed the importance of optimal management of side-effects in supporting adherence. Few studies examined the association between TKI type and adherence, most likely due to the fact that second generation TKIs had only just been introduced when the reviews were conducted. However, two studies showed that adherence to second generation TKIs was superior to imatinib (Almeida et al., 2010) and adherence to nilotinib was higher than to dasatinib (Wu et al., 2010^b).

Patient experience

Eliasson et al (2011) is referred to in several reviews regarding understanding reasons for non-adherence (Almeida et al., 2014; Gater et al., 2012; Jabbour et al., 2012^b). Unintentional non-

adherence, as described by patients, was most commonly due to forgetting, while intentional non-adherence was most frequently due to patients' decisions to omit TKIs due to side-effects (Eliasson et al., 2011). Noens et al (2009) found that self-reported quality of life and functional status had a relationship with adherence, and that improved adherence was associated with patient awareness of their disease and treatment.

The ADAGIO study (Noens et al., 2009) and Eliasson et al's (2011) study explored physicians' impact on patient adherence. Noens et al (2009) found that higher non-adherence was related to less years of physician experience and shorter duration of follow up appointments, also lower non-adherence was related to an increased number of CML patients seen per year and duration of first outpatient visit. Over half the patients in Eliasson et al's study (2011) discussed how advice from health care professionals (HCP) had "reinforced" occasional non-adherence, for example advising that "missing one or two" doses was acceptable. These studies point to the importance of the patient-practitioner relationship (Gater et al., 2012).

Adherence interventions

Several reviews discussed strategies to improve TKI adherence (Almeida et al., 2014; Gater et al., 2012; Breccia, Efficace and Alimena, 2011), including recommendations that HCPs provide individualised treatment plans, proactively manage adverse effects, and offer support and strategies to promote adherence. However, only Moon et al (2012) reported an actual intervention, which involved implementation of a patient counselling programme, with education, medication reminder texts and regular calls to offer support, all of which were associated with improved adherence compared to those who did not receive the intervention.

2.1.3 Summary

This synopsis of seven previous literature reviews provides an overview of studies and introduces the concept of adherence in CML. It shows a wide estimate of the level of adherence, likely due to the lack of a gold standard measure and consensus on the "cut off" level to define non-adherence. Review authors advised that future studies should use improved definitions of non-adherence and implement multiple measures. Nevertheless, it was consistently found, and accepted, that non-adherence had a negative impact on response and should be avoided.

Little evidence was available to support an association between patient characteristics and adherence, although there was some evidence of an association between lower adherence and co-morbidity. Treatment characteristics showed more consistent findings, yet little work was available regarding second generation TKIs. Interestingly, two studies found physician qualities, such as

experience and the advice given, could impact adherence. Some variables, such as age, gender and treatment type are not, or not easily, modifiable by practitioners. However, variables such as physician care are potentially adaptable so may have more relevance to practitioners. At this point in the literature though, there is little evidence to suggest what kind of interventions may effectively improve adherence, with only one study showing improvement due to an intervention.

My own new literature review, which follows, examines key aspects of the adherence literature published since January 2015, focusing on factors affecting adherence. This date was chosen as the search end date of the most recent review was 31st December 2014 (Alves et al., 2016). Using this date as the start of the search for literature in the new review gives an update on current knowledge since the old reviews, providing the reader with an up to date and relevant evidence base. Further aims of the new review were to discover whether new studies attempted to identify a 'gold standard' adherence measure or exact adherence 'cut off' point, to examine the association between adherence and survival outcomes or measure an adherence intervention

2.2 New literature review: What factors in contemporary research are associated with adherence to TKI medication in adults living with CML?

2.2.1 Literature review aim

The aim of this new literature review was to provide a revised report of studies examining the factors affecting adherence to TKIs for CML. It helped to inform qualitative interview schedules, locate the interview analysis findings, and also provide a quality assessment of the more current evidence. Finally, as a principal aim of the thesis is to provide practitioners with evidence that is relevant to clinical practice, I present the findings in terms of how modifiable the identified variables are likely to be by practitioners. For ease of reading, from this point I will refer to the previous literature reviews as the 'old reviews' to distinguish them from my 'new review'.

2.2.2 Methodology

A narrative review was chosen as an appropriate model for this new review. This approach relies on a narrative or textual method to summarise data, and offers a way to synthesise data that cannot be analysed using a meta-analysis, so suits this study (Aveyard 2010). As Greenhalgh, Thorne and Malterud (2018) argue, some review questions suit a narrative approach as they require a broad review and interpretation of the literature to enhance understanding of the topic, particularly if they are to be relevant to the complexity of clinical practice, as in the case of this new review. The search strategy, inclusion/exclusion criteria, and data extraction methods are detailed below:

Search strategy

In line with the literature review search strategy, search terms were based on the literature exploring different terms used for medication adherence described in the introduction (see section 1.5), in addition to database suggestions for alternative terms used for chronic myeloid leukaemia. As discussed, the start date of studies published since January 2015, was chosen as the end date of the most recent old review search strategy was 31st December 2014 (Alves et al., 2016). The PICOS criteria was used to frame the search strategy and inclusion/exclusion criteria (Richardson et al., 1995), although not all elements were included as they were not relevant (Centre for Reviews and Dissemination, University of York, 2008). The main objective of this literature review was broad; to describe factors related to adherence to TKIs used for CML. The subsequent PICOS criteria, search terms and inclusion/exclusion criteria are listed below:

Search terms

- Adherence *or* concordance *or* compliance

and

- Chronic myeloid leukaemia *or* Chronic myeloid leukemia *or* Leukaemia myelogenous chronic BCR-ABL positive

Published studies searched using

- MEDLINE (1946 onwards) (Ovid), CINAHL and Science citation index (Web of Science) databases

Database search limits

- Include studies published from January 2015 onwards

Inclusion criteria

PICOS criteria

Population: Studies of patients with chronic phase CML aged 18 and over.

Intervention (or exposure): Any factors relating to adherence to TKI medication.

Comparator: Not relevant

Outcome: Any clinical outcome including survival and molecular response.

Study type: Studies of any quantitative design.

Participants

- A diagnosis of CML
- Patients are in the chronic phase of CML at the time of the study
- Treatment with TKIs
- Adults aged 18 and over
- Males and females

Phenomena of interest

- Factors associated with adherence to TKI drugs in CML patients

Context

- Any geographical location.

Types of studies

- Studies measuring the factors associated with adherence to TKIs in patients with CML, including studies of any quantitative design.

Exclusion criteria

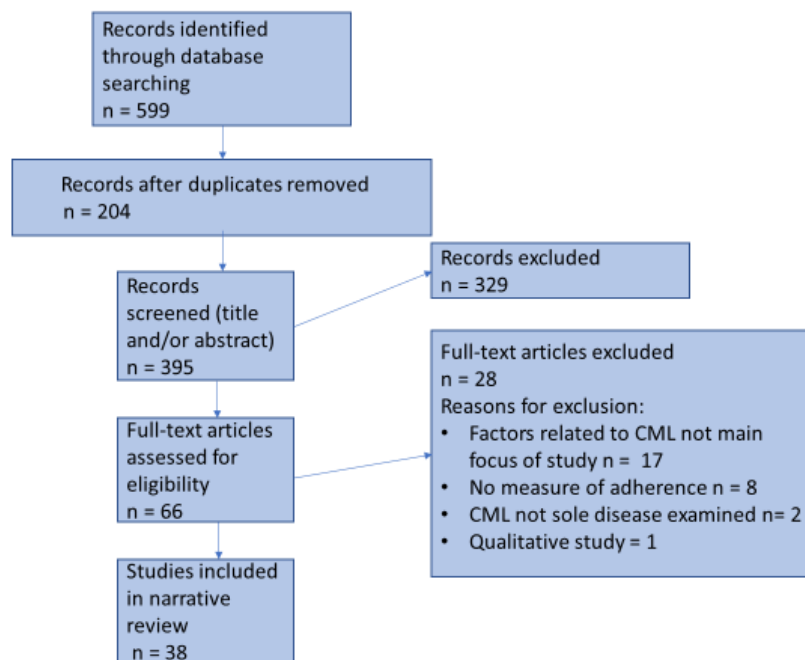
- Main aim is not the phenomena of interest
- No measure of adherence
- No measure of factors affecting adherence
- Case report/editorial/letter
- CML not the sole disease examined
- Children/adolescents
- Not in the English language
- Qualitative study
- Study protocol

Data extraction method

Data extraction involved recording data which described key features of the study such as design and setting, as well as the study methods and findings. A data extraction tool was created based on these criteria, the advice of relevant authors and previous literature reviews (Alves et al., 2016; Noens et al., 2014; Coughlan et al., 2013; Denison et al., 2013; Aveyard et al., 2010). Shown below are the headings used for data extracted from each study, and they form the basis of the summary of included studies shown in table 1:

- Author, year of publication
- Sample number/ data collection period/ follow up
- Country and setting
- Demographics
- Study design as described by authors
- Treatment
- Method used to assess adherence/cut off point/level of adherence
- Non-adherence effect on outcomes
- Factors related to adherence
- Quality

Figure 4 Prisma flow diagram: new literature review



Critical appraisal of included studies

In assessing study quality, I used the Mixed Methods Appraisal Tool (MMAT, Pluye et al., 2011; see appendix 1). I applied my own assessment of study type in order to classify this as defined by the MMAT (Pluye et al., 2011). The tool assesses the methodological quality of studies of mixed designs. “Quantitative descriptive (QD)” studies was used to define studies where adherence variables were described for the whole sample, and examined associations between groups (e.g. different TKIs, adherers/non-adherers), such groups being established after initial recruitment. “Quantitative non-randomised (QNR)” described studies where two groups had been sampled based on their characteristics at recruitment, and these characteristics described for each group. “Quantitative randomised controlled trial (QRC)” studies included those where patients were randomised into two groups in order to trial an adherence intervention. Finally, “Mixed Methods (MM)” studies included those where both quantitative and qualitative data collection techniques were used (although the qualitative element was excluded from the review). The majority of studies, 25, were of a QD design, followed by 9 QNR studies, 4 QRC and 1 MM. All cleared the first two screening questions of the MMAT, having well defined research questions and presenting data which reflected this. Whilst most QD studies reported an appropriate sampling strategy and measurements, there was a lack of clarity on whether the sample was representative of the study populations and if there was a satisfactory response rate. In contrast, QNR studies all reported a high level of methodological quality, but the QRC studies were mixed; one with a good report of the randomisation process, complete outcome data and a low dropout rate, and the remaining two including high dropout rates, not achieving complete outcome data or not describing the randomisation process. The MM study was of lower quality, with a lack of reporting on how representative their sample was, the use of an unvalidated adherence measure and a low response rate. All studies were included as they were of interest to the new review question. The MMAT results are shown in the last column of the study summary table 1, shown on the following pages. An answer to the two screening questions, then the following four study type specific questions are listed, followed by an overall quality percentage, a scoring system suggested by the authors.

2.2.3 Findings

The following section presents findings from the new review. A summary table of included studies and their findings is shown below in table 1.

Table 1 Summary of included studies: new literature review

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Al-Dewik et al 2016	n=36 Patients recruited between Jan 2010 – Dec 2012 Follow up (FU): not clear	Qatar, single national cancer centre male: 28 female: 8 age: 16-65	Prospective cohort study	Imatinib	MEMS (electronic medical events monitoring system) Morisky 9 item Medication Adherence Scale (MMAS) MPR (medication possession ratio) eMR (electronic medical records) MEMS ≤ 90% = non-adherent MMAS score of ≥ 11 = good adherence MPR ≥ 80% = high adherence eMR treatment response judged using 2013 ELN milestones MEMS mean adherence = 89%, 61% adherent and 39% non-adherent	Adherent patients significantly more likely to achieve optimal response when adherence measured by MEMS and MPR, but not significant using MMAS	No significant association of adherence with gender, marital status, educational level, lack of funds and side effects (using MMAS) Significantly high correlation between: MPR and MEMS MMAS and MEMS MPR and MMAS	QD Y Y Y CT Y CT 50%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Al-Dewik et al 2016 (cont.)					MMAS mean score = 10.6, 69% adherent and 31% non-adherent MPR mean score = 94%, 84% adherent and 16% non-adherent eMR: not fully reported			
Al-Ghazaly et al 2020	n=164 Oct 1999 – Oct 2018 Follow up (FUp): at least 12 months, median 46 months	Yemen, single haematology centre male: 93 female: 71 age: 16-80	Longitudinal cohort study	Imatinib or hydroxyurea then imatinib (imatinib not available until 2009)	MPR <90% = non- adherent 51.8% of sample non-adherent	Non-adherence significantly associated with worse PFS Adherence significantly associated with achievement of MMR at 12 and 46 months	Residence (rural) significantly associated with non-adherence No significant association: age, gender	QD Y Y Y CT Y CT 50%
Andrade et al 2019	n=120 Adherence measured for 360 days during time period of 2002 – 2014 (first year of treatment)	Brazil, single hospital centre male: 52 female: 41	Descriptive, observational and retrospective study	Imatinib	PDC (proportion of days covered: number of days covered by medication obtained divided by number of days patient is eligible to receive medication) ≥80% = adherent	Not measured	Disinterest in medical appointments and abandoning treatment significantly associated with non-adherence.	QD Y Y Y CT

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Andrade et al 2019 (cont.)	FUp: none	age: average 46			<80% = non-adherent PDC average = 86.52, 77.5% adherent and 22.5% non-adherent		No significant association: age, gender, educational level distance from hospital, parasitism and side effects.	Y Y 75%
Anderson et al 2015	n=124 Patients received TKI btw: 1 June 2010 – 31 January 2012 FUp: none	Canada, single cancer centre male: 78 female: 46 age: 18->90	Cross-sectional retrospective study (of pharmacy records)	Imatinib, dasatinib or nilotinib	MPR <90% = non-adherent 31% of sample non-adherent	Not measured	No concurrent medication, treated with imatinib, aged <50 significantly associated with non-adherence. No significant association: gender, residence, length of time on TKI, side-effects, not previously	QD Y Y Y CT Y CT 50%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Anderson et al 2015 (cont.)							treated with interferon	
Boons et al 2018	n=61 Study conducted between April 2013 – November 2015 FU: none	Netherlands: CML patients from the national Dutch CML advocacy group and/or those attending their conference male: 26 female: 35 age: average 53.9	Mixed methods study (quantitative questionnaire, qualitative interviews. Qualitative element excluded from this analysis)	Imatinib, dasatinib or nilotinib	Researcher derived questionnaire Reported missing tablets at least once a month of questionnaire = non-adherent 25% of sample non-adherent	Not measured	On at least second line of TKI significantly associated with non-adherence Gender, age, hospital type, time on treatment, side effects, type of TKI, level of concern, satisfaction and need for information/education not significantly associated with non-adherence	MM Y Y N/A N/A QD questions Y CT N N 25%
Buzaglo et al 2017	n=318 Pts registered online Oct 2013- June 2014	USA wide, online patient cancer experience registry	Not defined	CML medication: type not reported	Web based survey questions: frequency of missing a dose and how often pts postponed filling prescriptions	Not measured	34% reported financial costs effected household 'quite a bit' or more,	QD Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Buzaglo et al 2017 (cont.)	FUp: none	male: 103 female: 215 age: 18-85 (ave 56)			Suboptimal adherence=missed dose>once/month, or postponed filling prescriptions, or skipped dose to reduce healthcare spending 31% of sample had suboptimal adherence		16% postponed Drs appointments due to this. 45% at high risk of depression. Financial burden significantly associated with suboptimal adherence. High risk of depression not significantly associated with suboptimal adherence Financial burden significantly associated with suboptimal adherence in those at high risk of depression but not in those not at high risk of depression.	Y CT Y/N psychosocial/ financial measures Y 62.5%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Cantu-Rodriguez et al 2015	n=38 Adherence data collected August 2011 -June 2013 FUp: up to 301 days Disease response data appears to have been 7 years	Mexico, centre(s) not clear. Sample all under Glivec International Patient Assistance Program (GIPAP) male: 19 female: 19 age: 21-79 (median average 42)	Not defined	Imatinib	Pill Count (empty blister pack/box Simplified Medication Adherence Questionnaire (SMAQ) ≥85% mean adherence rate using pill count=adherent, <85%=non-adherent SMAQ: at least 1 questionnaire item indicated TKI had not been taken=non-adherent Mean average adherence rate 85.9% (not clear which method or both)	Achievement of MMR significantly associated with adherence	Longer duration of treatment significantly associated with poorer adherence Longer journey to medical centre to collect TKI significantly associated with better adherence No significant association between adherence and gender, age or years of education	QD Y Y CT CT N CT 0%
Clark et al 2020	n=2049 Data collected btw Jan 1 st 2017 – Dec 31 st 2017 FUp: 12 months	USA wide, medical insurance database data male: 1106 female: 943 age: mean average 47.9	Latent profile analysis (modelling technique for deriving adherence estimates over time)	Imatinib, dasatinib, nilotinib	PDC Adherence classed into different categories: Never adherent, Initially non-adherent becoming adherent, Initially adherent becoming non-adherent, or Stable adherent behaviour.	Not measured	“Never adherent” significantly associated with female gender, younger age, less concomitant medication, longer time on treatment, delayed initiation of	QD Y Y Y CT Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Clark et al 2020 (cont.)					<p>“Stable” adherent: no fluctuations in adherence >20%, i.e. PDC of 80% or more</p> <p>Average PDC = 87%</p> <p>Never adherent n = 145 Initially non-adherent becoming adherent n = 214 Initially adherent becoming non-adherent n = 181 Stable adherent behaviour n = 1509</p>		<p>treatment, or on a second generation TKI.</p> <p>Co-morbidity, financial burden, insurance type, relationship of patient to policyholder, and TKI starting dose not significantly associated with being “never adherent”</p>	75%
Cole et al 2019	<p>n=856</p> <p>Data collected from patients who started generic or branded imatinib on or after Feb 2nd 2016 and Aug 1st 2015 respectively.</p> <p>FUp: 180 days</p>	<p>USA wide, medical insurance database data</p> <p>Generic imatinib group n=119 male: 68 female:51 age: “<35”-64</p> <p>Branded imatinib group n=737</p>	Not defined	Generic or branded imatinib	<p>PDC</p> <p>Persistence (% of patients without a gap of ≥30 and ≥60 consecutive days without TKI therapy</p> <p>PDC: ≥80% and ≥90% calculated but not defined as “adherent”</p> <p>Persistence: calculated as above but “adherent” not defined</p> <p>Average PDC generic imatinib = 92%</p>	Not measured	<p>Patients who were initiated on generic imatinib had higher average PDC and higher persistence than those initiating branded imatinib</p>	<p>QNR</p> <p>Y</p> <p>Y</p> <p>CT</p> <p>Y</p> <p>Y</p> <p>75%</p>

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Cole et al 2019 (cont.)		male: 402 female: 335 age: "<35"-64			Average PDC branded imatinib = 85% Persistence generic imatinib: no gaps of ≥30 and ≥60 days: 87% and 94% respectively Persistence branded imatinib: no gaps of ≥30 and ≥60 days: 76% and 86% respectively			
Geissler et al 2017	n=2546 Recruitment period Sep 2012 - Jan 2013 FU: none	CML patients involved in the CML Advocates Network (umbrella organisation for 106 patient organisations from 81 countries). Recruited patients from Western and Eastern Europe, Anglo American countries, Asia, Latin-America, Near	Patient driven survey	Imatinib, dasatinib, nilotinib, "other".	8 item MMAS Researcher derived questions on adherence MMAS: <6 low adherence, 6-7.75 medium adherence, 8 high adherence. Researcher questions: cut off not defined MMAS: 32.7% highly adherent, 46.5% medium adherence, 20.7% low adherence	Not measured	Lower personal payments, male gender, older age, concomitant medication, living with family or partner, no side effects/well managed side effects, one dose of TKI per day, TKI type, satisfaction with information from doctor significantly more likely to be in medium adherence group. More than 2 years on	QD Y Y Y CT Y CT 50%

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Geissler et al 2017 (cont.)		and Middle East. male: 1334 female: 1212 age: 18-96					TKIs significantly lowered chance of being in medium adherence group. Male gender, older age, only taking one TKI per day, no side effects/well managed side effects, satisfaction with information from doctor significantly more likely to be in high adherence group. More than 2 years since diagnosis significantly lowered chance of being highly adherent. No significant association with adherence and phase of disease, taking part in a clinical trial,	

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Geissler et al 2017 (cont.)							having a routine and information provided on the risk of non-adherence.	
Hefner et al 2017	n=35 Data collection period not stated FU: none	Germany, single oncology outpatient clinic male: 14 female: 21 age: 22-87 (mean ave. 59)	Prospective descriptive study	Imatinib, dasatinib, nilotinib	Adapted Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) One positive answer to BAASIS=non-adherent Also, BAASIS incorporates a self-rated Visual Analogue Scale (VAS) of adherence 0-100% 51% of sample non-adherent 89-100 range on VAS	Not measured	Adherence not associated with age, gender, marital status, 1 st or 2 nd gen. TKI, side-effects, time since diagnosis, time since treatment initiated. Main coping strategies in group: spirituality and search for meaning. Patients were keen to follow medical instructions and have trust in oncologists (relationship with adherence not tested)	QD Y Y Y CT Y Y 75%

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Hosoya et al 2015	n=54 Pts enrolled btw Oct 2012 and May 2014 FU: none	Japan, single hospital male: 38 female: 16 age: 29-89 (median ave: 60)	Not defined (Cross sectional questionnaire survey)	Imatinib, dasatinib, nilotinib	Questionnaire (not clear but seems devised by researchers) Pts who responded that they took 100% prescribe dose=adherent <99% of prescribed dose=suboptimal adherence 68.5% of sample adherent	MMR achievement not significantly associated with adherence	No significant association btw TKI type, no. of daily tablets or dose, and adherence Suboptimal adherence significantly associated with longer length of treatment. Higher risk of non-adherence associated with "careless slips" (of medication) High cost of medication a low risk factor for reduced adherence	QD Y Y Y CT N CT 25%
Kapoor et al 2015	n=100	India, single cancer centre male: 63	Personal interview study	Imatinib	9 item MMAS MMAS ≥ 11 = adherent	Not measured	No concomitant drugs and no previous depression significantly	QD Y Y

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Kapoor et al 2015 (cont.)	Patients recruited Feb 2013 – May 2013 No FUp	female: 37 age: mean average 41.08			Median score = 12. 75% patients were adherent		associated with adherence. No significant association between adherence and gender, age, tobacco or alcohol use, educational level, financial assistance, employment, marital status, imatinib dose, time on treatment, side effects, or attendance at education sessions.	Y CT Y Y 75%
Kekäle et al 2015	n=86 Study period June 2012-September 2013 FUp: none	Finland, 8 hospital sites male: 45 female: 41 age: 19-79	Not defined	Imatinib, dasatinib, nilotinib	8 item MMAS Score of 8=highly adherent, 6-7.75=medium adherence, <6=low adherence MMAS: 23.3% highly adherent, 55.8%	Not measured	No significant association between adverse drug reactions (ADRs) and adherence ("because symptoms were equally common in each MMAS adherence class	QD Y Y Y CT Y Y

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Kekäle et al 2015 (cont.)					medium adherence, 20.9% low adherence		(high, medium, and low") Significant association between high number of ADRs and poorer quality of life	
Kekäle et al 2016	n=35 intervention group n=33 control group Pts enrolled June 2012-Aug 2014 FU: 9 months	Finland, 8 hospital sites Intervention group: male: 15 female: 20 age: 25-82 (median ave. 64) Control group: male: 19 female: 14 age: 31-83 (median ave. 59)	Randomised multicentre intervention study Intervention: Patient education including nurse face to face counselling and interactive information technologies Control: standard treatment	Imatinib, dasatinib, nilotinib	8 item MMAS Score of 8=highly adherent, 6-7.75=medium adherence, <6=low adherence Intervention group: At baseline 23% of group highly adherent At follow up 51% of group highly adherent Control group: Baseline 21% of group highly adherent Follow up 20% of group highly adherent	Not measured	Adherence was unchanged at 9 month follow up in half the intervention group, but improved significantly in 49% of this group (no significant change in control group) Adherence improved significantly more often in the intervention group than the control group Adherence dropped significantly in	QRC Y Y Y N/A N (79% completed study) N (20.9% dropout) 25%

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Kekäle et al 2016 (cont.)							49% of the control group at follow up	
Lam and Cheung 2016	Intervention group: n=44 Comparison group: n=225 Data collected between January 2009 – December 2014 FU: not specified	Northern California, 2 oncology clinics. (comparison group: from different oncology clinics within the same health care management plan) Intervention group: male: 60% female: 40% age: 29-83 (median average 57) Comparison group: male: 61.8% female: 38.2%	Retrospective comparative study Intervention: Pharmacist managed oral chemotherapy programme (including education, regular follow up and review of adherence side-effects etc.) Comparison group: No oncology pharmacist monitoring	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib. (imatinib patients only included in adherence and response analysis)	MPR ≥90% = adherent <90% = non-adherent Intervention group mean adherence: 94% Comparison group mean adherence: 88%	33 imatinib patients with adequate response results: 29 (87.9%) adherent, 4 non-adherent (12.1%). 9/29 adherent patients failed CCyR at 12 months, 2/4 non-adherent patients failed CCyR at 12 months (not a significant difference)	Significantly more patients with co-morbidity in the intervention group Adherence rate was significantly higher in the intervention group compared to the comparison group	QNR Y Y N Y CT Y 50%

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Lam and Cheung 2016 (cont.)		age: 18.4-92.8 (median average 54.9)						
Latremouille-Viau et al 2017 ^a	n=1022 Pts enrolled 2002-2014 FU: until end of insurance coverage or data availability	USA wide, medical insurance databases dasatinib group: male: 53.6% female: 46.3% age: mean ave 50.9 nilotinib group: male: 54.3% female: 45.7% age: mean ave 52.5	Retrospective cross-sectional cohort study	Dasatinib and nilotinib (as 1 st line therapy)	Proportion of days covered (PDC): days in possession of TKI during 6 or 12 month period divided by number of days in that period Cut off point not defined Mean PDC dasatinib group (6month period) 86.58% Mean PDC nilotinib group (6month period) 86.13% Mean PDC dasatinib group (12month period) 78.41% Mean PDC nilotinib group (12month period) 78.26%	Not measured	Adherence levels not significantly associated with TKI type (dasatinib or nilotinib) Dasatinib had significantly higher health care costs and higher risk of dose increase than nilotinib	QNR Y Y Y Y Y 100%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Latremouille-Viau et al 2017 ^b	n=1431 Patients enrolled between Jan 2006 – June 2015. FU: 13 months	USA wide, using medical insurance claims databases male: 766 (53.5%) female: 665 (46.5%) age: median average 55	Retrospective cohort study	Imatinib, dasatinib, nilotinib	MPR No cut off defined. ≥80% MPR: 74.7% of sample	Not measured	An increase of TKI adherence by 1% MPR was significantly associated with a decrease in inpatient (IP) admissions, IP days, emergency room (ER) visits and outpatient (OP) days An increase of one molecular monitoring test was significantly associated with an increase in MPR by 2.2% An increase of one molecular monitoring test combined with an increase of adherence by 2.2% was significantly associated with a decrease in the number of IP admissions, IP	QD Y Y Y Y Y 100%

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Latremouille-Viau et al 2017 ^b (cont.)							days, ER visits and OP days	
Leader et al 2018 ^a	n=58 (for covariates and EM) n=98 (BAASIS questionnaire) n=94 (physician reported VAS) Pts enrolled Oct 2013-Aug 2014 FU: 4 months	Israel, 4 hospital sites male: 69% female: 31% age: median average 60.5	Sub-analysis of a multiphase adherence research program	Imatinib, dasatinib, nilotinib	Electronic monitoring (MEMS: medical events monitoring system) Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) Visual Analogue Score (VAS) completed by physician MEMS: <95%=non-adherent BAASIS: Positive response to any item=non-adherent VAS: <10=non-adherent MEMS: median adherence 93% BAASIS: not reported VAS: median average 9	Not measured	Lack of membership in CML group, living alone and third line TKI treatment significantly associated with decrease in adherence BAASIS sensitivity 67%, specificity 71% Physician VAS sensitivity 78%, specificity 42%	QD Y Y Y CT Y 75%

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Leader et al 2018 ^b	n=47 Data collected October 2013-June 2015. Observation period of 4 months followed by 1-month intervention 3 months post intervention follow up	Israel, 4 hospital sites male: 69% female: 31% age: median average 60.5	Quasi-experimental pre-post intervention study Intervention: behavioural change techniques, including motivational interviewing and feedback on adherence	Imatinib, dasatinib, nilotinib	Electronic monitoring (MEMS: medical events monitoring system) ≥90% = high adherence <90% = suboptimal adherence Post intervention adherence (MEMS %) not specified	Not measured	Odds of taking TKI daily post intervention were 58% higher post intervention than pre-intervention 1.5% improvement in correct daily dosing post intervention, but in those with <90% adherence at baseline this improvement was 8.5% No significant decrease in intervention affect 90 days post.	QNR Y Y Y Y Y 100%
Maeda et al 2017	n=20 Data collection period and FUp: not reported	Japan, single centre Gender and age: not reported	Not defined	Imatinib or nilotinib (used as 2 nd line)	Morisky 9 item Medication Adherence Scale (MMAS) MPR MMAS score of 11 or above = adherent	Not measured	Adherence (MMAS) improved significantly in 2 nd line nilotinib users compared to imatinib	QD Y Y CT Y

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Maeda et al 2017 (cont.)					Adherence level of sample not reported		Imatinib related adverse events disappeared when nilotinib started, but new adverse events occurred. QOL improved significantly on nilotinib. No significant difference in MPR between the imatinib/ nilotinib patients	CT CT 25%
Maeda et al 2019	n=20 Data collection period not reported FUup: none	Japan, single hospital centre male: 12 female:18 age: 28-80	Questionnaire survey	Imatinib, nilotinib (switched from imatinib)	9 item MMAS MMAS \geq 11 = adherent Level of adherence in group not reported.	Higher adherence significantly associated with improved molecular response	Switching from imatinib to nilotinib significantly associated with higher adherence Adverse events decreased after switching from imatinib to nilotinib Improved QOL in switched	QD Y Y Y CT Y CT 50%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Maeda et al 2019 (cont.)							nilotinib group than imatinib group	
Moulin et al 2017	n=23 Data collection period not stated FU: 4 months	Brazil, single hospital Gender and age: not reported	Not defined (intervention study using questionnaire) Intervention: Pharmacist monitoring Seemingly all 23 patients received the intervention, although a control group is referred to in molecular monitoring comparisons, and 'non-monitored' group in the abstract however no description provided.	TKIs not specified	Morisky Medication Adherence Scale (MMAS) (item number not clear) Brief Medication Questionnaire (BMQ) Other questionnaires: adherence, potential to adherence and symptoms/ complaints (not clear if devised by researchers) MMAS and BMQ: cut off not defined Questionnaire to evaluate adherence: 0=adherent, 1-4=non-adherent. Questionnaire to evaluate potential to adherence: "Yes" answers to any questions= non-adherent	Increased rate of MMR after pharmacy intervention	No. of non-adherent patients decreased 8-0, no. adherent patients increased 15-23 post intervention No. symptoms and complaints decreased from 11 to 5 post intervention	QNR Y Y CT Y (MMAS BMQ)/N (others) CT CT 12.5%

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Moulin et al 2017 (cont.)					No. of non-adherent patients decreased 8-0, no. adherent patients increased 15-23 post intervention			
Mulu Fentie et al 2019	n= 147 Pts enrolled who started treatment Oct 2016-Sep 2017 FU: 3 months	Ethiopia, single centre (where all patients with CML in the country are referred and are followed up) male: 59.2% female: 40.8% age: 14-74 (mean ave. 37.8, median ave. 36)	Prospective cohort study	Imatinib	Morisky 8 item Medication Adherence Scale (MMAS) Questions about reasons for adherence "collected from patient chart" MMAS: Score of 8=highly adherent, ≥6 - <8 =medium adherence, <6=low adherence 55.5% of sample highly adherent 29.2% of sample medium adherence	Patients who had high or medium adherence were approx. 9 and 7 times (respectively) more likely to achieve CHR than those with low adherence	Adverse drug events, rural residence, lower income, lack of employment, presence of co-morbidity, significantly associated with lower adherence. Presumably, gender and educational level had no significant association with adherence	QD Y Y Y CT Y CT 50%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Mulu Fentie et al 2019 (cont.)					15.3% of sample low adherence		Main reason for non-adherence: adverse drug events, then in order: boredom with taking drugs, feeling well without treatment, lack of trust in drug efficacy (due to religious belief). Forgetfulness and lack of drug information least common reasons.	
Okumara et al 2015	n=151 Patients enrolled who were seen by pharmacists in 2014 FU: not reported	Brazil, single hospital centre male: 89 female: 62 age: ave. 51.5	Retrospective study (of pharmacy intervention documentation)	Imatinib, dasatinib, nilotinib	Pharmacist identified cases of non-adherence through clinical record review and questions to patient Based on answers to questions about adherence: non-adherent Optimal BCR/ABL, sustained MMR/CMR= adherent	Not measured	High school level education and raised BMI significantly associated with non-adherence. Gender, age, residence, employment, alcohol/smoking, also other levels of education (basic school, college) not significantly	QD Y Y Y CT N CT 25%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Okumara et al 2015 (cont.)					78.8% of sample adherent		associated with adherence. Reasons for non-adherence in patient group with BMI and education risk factors: lack of organisation (forgetting) and adverse drug events	
Phuar et al 2020	n=863 Patients newly diagnosed between 1 st April 2011 – 31 st Dec 2014 FU: not clearly defined	USA wide, medical insurance database data male: 464 female: 399 age: 18-64	Not defined	Imatinib, dasatinib, nilotinib	PDC PDC ≥ 80% = adherent 41.1% of sample adherent	Not measured	Non-adherent patients experienced significantly more medical costs and non-TKI pharmacy costs. Adherent patients experienced significantly more TKI pharmacy costs but were significantly less likely to have all	QD Y Y Y CT Y Y 75%

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Phuar et al 2020 (cont.)							<p>cause or CML specific hospitalisations</p> <p>Those of older age, regional residence, chronic disease phase, high CML complexity, no dose decrease, less time to treatment initiation, on 2nd generation TKI significantly more likely to be adherent.</p> <p>Health plan type or provider, gender, not significantly associated with adherence</p>	
Rychter et al 2017	<p>n=140</p> <p>Data collection dates not clear</p> <p>FUp not reported specifically but appears to be more than 2 years</p>	<p>Poland, 4 hospital centres</p> <p>male: 70</p> <p>female: 70</p> <p>age: ≥18 - >65</p>	<p>Not defined (questionnaire study)</p>	<p>Imatinib. Dasatinib, nilotinib</p>	<p>Questionnaire questions to measure adherence. Not clear if devised by researchers.</p> <p>Cut off point not reported</p>	<p>Not measured</p>	<p>In the month prior to follow up appointment:</p> <p>Aged ≥65 and presence of co-morbidity significantly associated with</p>	<p>QD</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>CT</p>

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Rychter et al 2017 (cont.)					<p>39% of sample reported skipping at least 1 dose in the month prior to follow up doctor's appointment</p> <p>51.4% reported skipping doses from the start of treatment until follow up appointment</p>		<p>increased improved adherence.</p> <p>No significant association btw gender, education, residence, marital status, or adverse effects and adherence.</p> <p>Throughout treatment duration:</p> <p>Secondary school educational level significantly associated with non-adherence compared to basic or higher educational level.</p> <p>Non-adherence significantly associated with longer duration of treatment</p> <p>Patients over - estimated their</p>	<p>N</p> <p>CT</p> <p>25%</p>

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Rychter et al 2017 (cont.)							adherence when their report of following of doctor's instructions compared to reports of missing doses. 93.6% received adequate instructions about adherence	
Sacha et al 2017	n=144 Pts enrolled June 2010-June2012 FU: 12 months	Poland, 23 centres male: 54 female: 90 age: 24-86 (mean ave. 57.8)	Prospective observational study	Nilotinib (as 2 nd line treatment)	Morisky 4 item Medication Adherence Scale (MMAS) Physician assessed MMAS also MMAS score of 0 highly adherent, 1-2 medium adherence, 3-4 low adherence Patient reported MMAS: 83.2% of sample highly adherent and 1.7% of sample low adherence at baseline, 92.4% highly adherent and 0% low adherence at 12 months.	Not measured	Agreement btw physicians and patients MMAS: significantly correlation. QOL (adverse effects) significantly negatively associated with adherence Men significantly less likely to be adherent than women Those living with family more	QD Y Y Y CT Y Y 75%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Sacha et al 2017 (cont.)							likely to be adherent No significant association btw drug schedule, satisfaction with medical care , age and level of education with adherence	
Santeroli et al 2019	n=123 Intervention group=45 (out of original total). Control: same 45 patients (before/after diary intervention) Data collected Jan 2007-March 2016 Intervention (medication diary+pharmacy support) from 2012 to up to 4	Italy, single hospital centre male: 82 female: 51 age: 22-79 (median ave. 55) (intervention group characteristics not specified)	Prospective observational study (with intervention)	Imatinib, dasatinib, nilotinib	Intervention group: Patient completed treatment diary plus Received daily dose (RDD)/prescribed daily dose (PDD) Diary: an uncompleted line= non-adherence. Uncompleted line/completed line=adherence Cut off point for RDD/PDD not specified	Not measured	Adherence significantly improved for intervention group once diary/pharmacy support implemented Main cause of non-adherence: forgetfulness. Adherence calculated using diary and RDD/PDD were similar	QNR Y Y Y Y NA CT 50%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Santeroli et al 2019 (cont.)	years. Adherence in the same patient with/without diary/intervention compared				Diary: 97.4% adherence (presumably average %) RDD/PDD: 93.6% adherence (presumably average %) Period prior to intervention (i.e. no diary or pharmacy support): 86.5% adherence (presumably RDD/PDD average %)			
Sawicki et al 2019	n=279 intervention group n=279 control group Patient enrolled from Feb 2016-December 2016 Patients followed up for 365 days	USA wide, using claims data from a speciality pharmacy service Intervention group: male: 145 female: 134 age: mean average 53.3% Control group:	Retrospective observational cohort study Intervention group: 2 way clinical messaging (personalised messages with opportunity to ask questions, communicate difficulties, request OPA etc.) Control Group: 1 way texting usual care (refill reminders,	Imatinib, dasatinib, nilotinib, bosutinib	MPR and Persistency Optimally adherent = >85% MPR Gap in persistency = >60 days gap between prescription refills Intervention group: MPR 73.9% adherence, 53.4% of group optimally adherent Persistency average gap 8.0 days Control group:	Not measured	Adherence (MPR) significantly better in intervention group compared to control Persistency after 12 months similar in both arms Gaps days similar between groups but average length of time on therapy significantly	QNR Y Y Y Y 100%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Sawicki et al 2019 (cont.)		male: 153 female: 126 age: mean average 54.4	prescription status etc.)		MPR 66.3%, 43.7% of group optimally adherent Persistency average gaps days 7.8 days		longer in intervention group than control. 41% whole group remained on TKIs at end of 12 month period	
Shen et al 2018	n=836 Data collected from 2007-2012	USA wide, national cancer registry and medical insurance data Non adherers: male: 123 female: 121 age: ≤70 105 >70 139 Adherers:	Not defined (retrospective study of cancer registry/medicare D insurance plan data)	Imatinib, dasatinib, nilotinib	Proportion of days covered (PDC) <80% = non-adherent 29% Non-adherent	Not measured	Patients with heavily subsidised plans significantly more likely to be non-adherers than those with no subsidy, despite them having very low out of pocket costs (OOP) Patients with higher out of pocket (OOP) costs more likely to be non-adherers	QNR Y Y Y Y Y 100%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Shen et al 2018 (cont.)		male: 314 female: 278 age: ≤70 290 >70 302					In those without subsidies: significantly more likely to be non-adherers if aged >70 and having a medicare prescription drug plan. Residence not significantly associated with non-adherence	
Smith et al 2016	n=659 Pts enrolled from 2006-2012 FU: until date of death, end of insurance coverage or end of data availability	USA wide, national medical insurance records male: 250 female: 409 age: 65-80+ (ave. 76)	Retrospective cross-sectional cohort study (of medical insurance records)	Dasatinib and nilotinib	MPR ≥ 85%=adherent Adherence in first 6 months study: Dasatinib average MPR 81% Nilotinib average MPR 79%	Mortality risk for pts on nilotinib significantly lower than for those on dasatinib	Proportion adherent pts significantly higher amongst nilotinib pts than dasatinib at 12 months Dose increases significantly more likely in pts on dasatinib	QD Y Y Y Y Y 100%
Tan et al 2020	n=65 intervention group	Malaysia, two hospital centres	Prospective, parallel, randomised controlled trial	Imatinib, dasatinib, nilotinib, ponatinib	MPR MPR>90% = optimal adherence	Proportion of patients achieving MMR significantly	Proportion of patients with optimal adherence significantly	QRC Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Tan et al 2020 (cont.)	n=64 control group Patient recruited March 2017-Jan 2018 Trial conducted March 2017-Jan 2019 Intervention lasted 6 months FU: 12 months	Intervention group: male: 35 female: 30 age: median average 44.5 Control group: male: 41 female: 23 age: median average 40.5	Intervention: 6-month medication management service (inc. pharmacy led face to face and telephone calls to provide information, medication aids, support with side-effects, medication review) Control group: Usual pharmacy services		Optimal adherence at baseline, 6, and 12 months: Intervention group: 50.8, 81.5, 72.6 % of group Control group: 60.9, 56.3, 60.3% of group.	greater in intervention arm than control arm at 6 months but not at 12 months. Further analysis (taking into account confounders) showed the intervention was significantly associated with the proportion achieving MMR	greater in intervention arm than controls at 6 months, but no significant difference at 12 months Longer duration of TKIs and increased number of concomitant medications significantly associated with lower adherence 6 of 20 QOL measure subscales were significantly improved in intervention group	Y NA Y Y 75%
Tsai et al 2018	n=58 Data collected Jan 2015 – June 2015 No FU	Taiwan, single centre study male: 39 female: 19	Retrospective cross-sectional study	Imatinib, dasatinib, nilotinib	Morisky 8 item Medication Adherence Scale (MMAS) MMAS score of <6 low adherence, 6-7	Adherence to TKIs significantly associated with 12 month MMR	(researcher adherence questions used in this analysis) Older age and being married	QD Y Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Tsai et al 2018 (cont.)		age: 20-83 (median average 51)			medium adherence, 8 high adherence. Also 2 questions added by researchers: about whether the appearance of side-effects or treatment information altered medication adherence Median average adherence: 6 (medium) 31% high adherence, 37.9% medium adherence, 31% low adherence		significantly associated with better adherence. Gender, co-morbidities, concomitant drugs, duration of TKI treatment and TKI type not significantly associated with adherence Presence of side-effects not significantly associated with adherence Lack of treatment information significantly associated with non-adherence	CT N Y 50%
Unnikrishnan et al 2016	n=221 Data collected March 2014-August 2014 (+6months for	India, single centre male: 133 female: 88	Not defined (cross sectional questionnaire study)	Imatinib	Morisky 8 item Medication Adherence Scale (MMAS) MMAS score of <8=non-adherent, 8=adherent	112 patient had molecular testing during data collection period + 6 months:	Global health status (on QOL questionnaire) significantly higher in adherent group	QD Y Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Unnikrishnan et al 2016 (cont.)	molecular test results) No FUp	age: 17-68 (median average: 39)			Median MMAS score 7 (medium adherence) 45% adherent, 55% non-adherent	Undetectable BCR-ABL significantly associated with adherence. None of the non-adherent group achieved undetectable BCR-ABL	Non-adherence associated with greater symptom burden No significant association between religion, marital status, education, occupation, income, frequency of hospital visits, awareness of diagnosis, awareness of therapy, duration of therapy and adherence	CT Y CT 50%
Ward et al 2015	n=368 met criteria for adherence analysis n=133 of above group met criteria for health care	USA wide, using medical insurance plan data Initiated on 1st generation	Retrospective observational cohort study	1 st generation TKI group: imatinib 2 nd generation TKI group:	PDC ≥85%=adherent <85%=non-adherent 1st generation: mean PDC 77%	Not measured	No significant difference in adherence between groups 2 nd generation group associated with increased inpatient days	QNR Y Y Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Ward et al 2015 (cont.)	utilisation and cost analysis Patient enrolled between June 2010 and December 2011 FU up 1 year	TKI (imatinib) group: male: 112 female: 125 age: mean average 69.9 Initiated on 2nd generation TKI (dasatinib or nilotinib) group: male: 57 female: 74 age: mean average 67.2		dasatinib or nilotinib	2 nd generation: mean PDC 68%		but no other significant difference in health care services utilisation between groups Healthcare costs significantly higher in 2 nd generation group (higher pharmacy costs)	Y Y 100%
Winn et al 2016	n=393 Patients enrolled between 2007 and 2011 FU up: 180 days	USA wide, national cancer registry and medical insurance data No TKI initiated within 180	Not defined (retrospective study of registry and insurance plan data)	Imatinib, dasatinib and nilotinib	PDC >80% adherent 61% of group adherent (in those who had initiated a TKI)	Not measured	68.2% of whole group initiated a TKI within 180 days of diagnosis Later year of diagnosis, metropolitan residence, and age over 80 associated with	QNR Y Y Y Y

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Winn et al 2016 (cont.)		<p>days group (and alive at 180 days):</p> <p>male: 44.7%</p> <p>female: 55.3%</p> <p>age: median average 79.56</p> <p>TKI initiated within 180 days group:</p> <p>male: 48%</p> <p>female: 52%</p> <p>age: median average 74.87</p>					<p>reduced initiation of TKI (in those alive at 180 days)</p> <p>No significant association between TKI initiation and cost sharing subsidies (in those alive at 180 days)</p> <p>Aged 60-69 and later year of diagnosis significantly associated with improved adherence.</p> <p>No significant association with adherence and cost sharing subsidies, marital status, gender, poverty level or year of diagnosis in those initiated on TKI</p>	<p>Y</p> <p>100%</p>

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Yanamandra et al 2017	n=333 Patients recruited from CML education day September 2015, data collection dates not clear No FUp	Northern India, single tertiary centre male: 59% female: 41% age: 12-83 (median average 42)	Cross-sectional observation study	Imatinib	Morisky 9 item Medication Adherence Scale (MMAS) and physician assessed adherence (by looking at case records) ≥11 score on MMAS = good adherence <11 score on MMAS = poor adherence Physician adherence cut off not defined MMAS: 54.95% of group had good adherence, 45.05% had poor adherence. Physician assessed adherence: 90.39% adherent, 9.61% non-adherent	Initial statistical testing showed no relationship between MMR and adherence, bivariate analysis by logistic fit testing showed significant association between MMR and adherence	Significant association between adherence and enrolment in patient assistance program (helping access to medications) No significant association between adherence and: age, gender, treatment duration, frequency and dose of treatment, education, income, social support, knowledge of medicine and disease, concomitant medications and tertiary institute factors. 14% never received	QD Y Y Y CT Y CT 50%

Author /year	Sample number/ data collection period/ follow up	Country and setting Demo-graphics	Study design as described by authors	Treatment	Method used to assess adherence/cut off point/level of adherence	Non-adherence effect on outcomes	Factors related to adherence	Quality
Yanamandra et al 2017 (cont.)							<p>information on their disease</p> <p>53.7% of patients had suboptimal knowledge about disease</p> <p>Of those with disease knowledge, 91% received information from their treating physician</p>	

Study characteristics

Thirty eight quantitative studies from January 2015 onwards were included. These were published throughout this period with a peak in 2017 (ten publications). The research spanned five continents (Asia, Africa, North America, South America and Europe), with one study including worldwide data. The largest group (thirteen) originated from North America. Compared to studies published pre-2015, the recent work addresses second generation TKIs, new adherence interventions, and patient experience. The majority of research from the USA and Canada were retrospective database studies, often examining the relationship of adherence with healthcare costs and second generation TKIs. Asian studies tended to include more descriptive accounts of adherence variables alongside questionnaires examining the patient experience, while the latter were also the most common in European work. Some studies reported on adherence interventions and their effectiveness, which came from all three areas, and others. Study design was reported in most studies, although several did not define the research type.

Descriptions of studies varied, some more comprehensive than others and some appearing to contain inaccuracies in their description, for example, Smith et al (2016) describe their study as a retrospective cross-sectional cohort design. However, patients were followed up for up to six years and the two groups examined (dasatinib or nilotinib) were established after recruitment, giving the appearance of a descriptive, correlational study. Where specified, study design descriptions included a report of whether the study was retrospective (n=8), cross-sectional (n=1), prospective (n=6) or an intervention (n=6) study.

Adherence measures

Similar to findings in the old reviews, the rate of non-adherence and adherence in this new review varied widely, from 0-55%, and 20-94%, respectively. Some studies used an average level of individual adherence rather than reporting the percentage of the group who were adherent/non-adherent, the average being 66.3%-97.4%. As previously reported, these disparities are likely due to differing adherence measures and cut off points. Adherence measures used by the studies in this review included objective, subjective and combined methods; the three most common being the objective medication possession ratio (MPR) (n=8) and proportion of days covered (PDC) (n=8), and the subjective Morisky Medication Adherence Scale (MMAS) (n=13).

Of the eight studies using the MPR, six used it as the only adherence measure, and all eight studies using PDC had this as their sole measure. Use of the PDC to quantify adherence has increased since the old reviews and is considered a more accurate measure than MPR (Crowe, 2015) as it prevents over-estimation of adherence due to early prescription collection, instead allowing for this, which is important if the patient takes multiple medications. Those using the MPR or PDC were frequently retrospective studies using databases linked to medical insurance health plans, originating in America, which would seem a logical choice where large datasets of pharmacy and medical data were available. Other objective measures included the medication event monitoring system (MEMS) and pill count, although these were rarely used, and TKI plasma level measurement was not used at all.

Despite widespread use, often in combination with other measures, studies used different versions of the MMAS or independent adaptations, meaning the number of questionnaire items ranged from 4 to 9, with most using the 8 or 9 item MMAS. The questionnaire was often used in studies examining the association between adherence and outcome, in addition to sociodemographic and Quality of Life (QOL) variables. The other main subjective measures of adherence employed were various questionnaires/questions designed by the research team; the validity and reliability of which were unknown and comparison to other adherence studies was difficult. However, such methods allowed researchers to hone in on their areas of interest, which may not be possible using existing measures. Other subjective methods used in some studies were the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS), the Brief Medication Questionnaire (BMQ) and the Simplified Medication Adherence Questionnaire (SMAQ), in addition to medication dairies and visual analogue scales (VAS).

In the summary of old reviews, the authors advised that future studies should use multiple methods to assess adherence in the absence of a 'gold standard' tool. Eight of the thirty eight studies in this new review used multiple methods. One intervention study mixed objective measures which included the MPR. Three studies mixed subjective methods of assessing adherence, all included the MMAS and either a researcher devised questionnaire or the BMQ.

Four studies in the new review, however, used a combination of objective and subjective adherence measures. Three of these again examined sociodemographic variables and adherence, and the fourth compared adherence to 2nd generation TKIs in an intervention. Two studies examined the correlation between adherence measures. Cantu-Rodriguez et al (2015) found a significantly good correlation between the objective pill count and the subjective SMAQ commenting that imatinib plasma levels would be the most accurate method, but were too expensive and inconvenient to use. Al-Dewik et al (2016) found a high correlation between MMAS and MEMS, MPR and MEMS, and MPR and MMAS.

Choice of measurement tool may also depend on study design, as is illustrated by the frequent use of MPR in retrospective studies of large datasets, whereas questionnaires may be more suited to cross sectional studies of patient experience. Furthermore, the reliability of objective methods may also be questioned, as it was by authors of the old reviews, for example MPR only confirms medication was collected, but not that it was taken. Overall, little progress is evident in this new review of the development of a gold standard measure, or consistent use of multiple assessment measures. This is complicated further by varied adherence cut off levels described by authors using the same measure, and is discussed in the following section.

Cut off/definition of adherence and non-adherence

Most authors defined adherence, non-adherence or degrees of adherence, depending on the results of their chosen measure, and report this in their methods. In the earlier summary of the old reviews, Gater et al (2012) and Noens et al (2014) advocated research to accurately define adherence and “what it means to be adherent”, including consistent cut off levels. However, studies in this new review continue to show some variance in cut off levels used for the common measures; the MPR, PDC and MMAS. Definitions of adherence or optimal adherence using the MPR varied from >80% to >90%. Some studies did not justify their choice of cut off level, although others did, generally basing this definition on previous studies, although usually only one study was quoted and there was little consistency between them. Overall, the use of different cut off points complicates comparison between studies. There seemed a little more consistency, however, in the adherence cut-off point described by studies using the PDC, with five of the eight classifying a score of $\geq 80\%$ as adherent. Some variance remained though with three studies either quoting a different cut off point or not defining this clearly.

There was some variation amongst authors using the 8 item and 9 item versions of the MMAS in how the cut off level of adherence for each was defined, studies either using a range of low, medium or high adherence, or placing participants into an adherent or non-adherent group. These were the most common versions used, although one study used the 4 item format (Sacha et al., 2017) and one did not specify (Moulin et al., 2017). It is unclear why different versions were used, although the Sacha et al (2017) study reported using an adapted version for the Polish language. Several justify use of the MMAS by citing its validity and use in other studies and when defining cut off levels, most citing Morisky’s works as a reference for their choice.

Finally, the fourth most commonly used method to assess adherence, the researcher devised questionnaire, was used in six studies. Four of these did not specify an adherence cut off, while the remainder set the level high, citing previous literature to justify their definition. Overall, there was a

lack of consistent cut off points or definitions of adherence in the literature, making comparison between studies difficult. Moreover, the optimum course of action may be to apply a CML specific, clinically relevant level of non-adherence, as cited in established literature.

Consequences of non-adherence

Disease response

Ten studies investigated the association between adherence and disease response. Commonly this was a measurement of molecular response, reflecting the long-term monitoring method for most CML patients. Seven studies found that non-adherence was associated with a reduced achievement of major or complete molecular response (MMR/CMR). Non-adherent patients were also less likely to achieve complete cytogenetic response (CCyR) and complete haematological response (CHR) which confirms findings from the old reviews. Interestingly, three studies contradicted these findings, reporting no significant association between molecular or cytogenetic response and adherence. Lam and Cheung (2016) explained this may be due to their small sample size and the very high adherence level (97%), which may have meant differences in response were not detectable in such a small group of non-adherers. Al-Dewik et al (2016), however found that adherence was significantly associated with molecular response when measured by MEMS or MPR, but not with the MMAS.

Survival

Two studies calculated survival risk, compared to only one in the old reviews, with both having significant follow up periods (Al-Ghazaly et al., 2020; Smith et al., 2016). Al-Ghazaly et al (2020) concluded that non-adherence was significantly associated with worse progression free survival (PFS) and Smith et al (2016) compared two 2nd generation TKIs, finding that mortality risk was significantly reduced in those taking nilotinib compared to dasatinib. This study is one of several exploring second generation TKIs and adherence, showing a progression in knowledge since the old reviews.

Factors affecting adherence

Study findings which reported on variables associated with adherence are described in this section under the headings: 'non-modifiable' and 'modifiable'. This highlights the pragmatic aim of this thesis. Many studies have contributed to the evidence regarding adherence variables since the old reviews, with notable advances in those examining the patient experience and adherence interventions. Non-modifiable characteristics are initially described, and although factors such as

treatment dose may be perceived as modifiable by practitioners, current guidance does not advise change (TKI dose or type), based on poor adherence alone.

Non-modifiable factors

Patient characteristics

Consistent with findings from the old reviews, evidence for the impact of age on adherence remains contradictory, with nine of sixteen studies reporting no significant association, and seven finding a significant association; results from these latter studies agreeing that those people aged around sixty years and over had improved adherence, or that those under 50 were more likely to be non-adherent. Whereas the old reviews also found contradictory evidence about the association between gender and adherence, the findings from this new review suggest no association between the two. Of eighteen studies measuring adherence and gender, fifteen found no significant association.

Evidence of an association between concomitant medications or co-morbidity, and adherence, remains unclear in this new review. Two of six studies examining concomitant medications found no significant association with adherence. The remainder reported a significant association of concomitant medication and adherence (Geissler et al., 2017), less concomitant medications and increased non-adherence (Clark et al., 2020; Anderson et al., 2015), and no concomitant drugs and adherence (Kapoor et al., 2015). Whilst two studies found no significant association between co-morbidity and adherence, one found that co-morbidity was associated with reduced adherence (Mulu Fentie et al., 2019) and another that it was associated with improved adherence (Rychter et al., 2017).

Six of nine studies examining economic factors related to TKI non-adherence were retrospective, USA based and analysed large datasets, using the MPR or PDC as measures. The remaining three studies were from Japan (Hosoya et al., 2015), India (Yanamandra et al., 2017) and a USA study which used a cross sectional patient survey (Buzaglo et al., 2017). Two studies, and their USA bias, produced findings that were unchanged from the old review; describing how improved adherence was associated with lower inpatient stays, urgent appointments and healthcare costs (Phuar et al., 2020; Latremouille-Viau et al., 2017^b). Costs to the patient were of particular interest to researchers. Yanamandra et al (2017) found that those registered on a patient assistance programme to access drugs in India had improved adherence, and Buzaglo et al (2017) reported, in their large USA based online survey, that the financial impact on patients' households was significantly associated with poorer adherence in those at high risk of depression. Finally, and suggesting progress since the old reviews, two studies investigated healthcare costs and second generation TKI drugs. Ward et al

(2015) found healthcare costs for nilotinib users significantly greater than those on 1st line imatinib, due to pharmacy costs and more inpatient days. However there were no other significant differences in healthcare costs. Latremouille-Viau et al (2017^a) also reported that dasatinib incurred significantly higher healthcare costs than nilotinib.

Studies from the USA investigating the impact of out of pocket costs/co-payments and cost sharing subsidies on adherence suggest a more complex picture in this new review than that presented in the old reviews. In the USA, a co-payment for TKI drugs reflects a fixed amount payable by the individual to their service provider, as set out in their medical insurance plan. This “out of pocket” cost, which forms part of the “cost sharing” burden of medical insurance on patients, can be high for oncology drugs and is dependent on the type of insurance cover (Dusetzina et al., 2014). Medicare D is the USA federal government programme designed to support individuals to cover the cost of self-administered drugs through insurance premiums. Co-payments on this scheme may still be high (Winn, Keating and Dusetzina, 2016), however subsidies to assist payment for these costs are available to some (Shen et al., 2018). One study found that patients in the USA with higher out of pocket payments were significantly more likely to be non-adherent (Shen et al., 2018). Whilst it seems logical that these higher payments may be related to worse adherence, Winn, Keating and Dusetzina (2016) found no significant association between cost sharing subsidies, and adherence. Furthermore, Shen et al (2018) found that those with a higher subsidy were significantly more likely to be non-adherent and Hosoya et al (2015) found high medication costs were a low risk factor for non-adherence. Whilst this difference may be due to a smaller sample size (Winn, Keating and Dusetzina, 2016), it seems possible that despite efforts to decrease payments for some, this may not improve adherence, which may be underpinned by more complicated multifactorial influences (Shen et al., 2018). These latter studies question associations found in other studies and the old reviews, between objectively measured increased costs to the patient and worse adherence.

New in this review are studies concerned with many other socioeconomic variables, the three most frequent characteristics reported being education, residence and marital status. However, there is little evidence that such variables impact on adherence, suggesting perhaps that the socioeconomic differences in CML survival in the UK (Smith et al., 2014), if related to adherence, are more complex and cannot be explained by a single socioeconomic characteristic. Of ten studies examining an association between education and adherence, eight found no significant relationship. The two studies reporting an association had similar, inconclusive findings. Okumara et al (2015) and Rychter et al (2017) found that having a high school, or secondary school level education was significantly associated with non-adherence, whereas both studies showed no significant association between a lower (e.g. basic) or higher level (e.g. college) of education and adherence.

Al-Ghazaly et al (2020) and Mulu-Fentie et al (2019) reported a significant association between rural residence and non-adherence, whereas Cantu-Rodriguez (2015) found that those with a longer journey to the medical centre were more adherent than those living closer, and Phuar et al (2020) observed an association between residential region of the USA and adherence. However, five further studies found no significant association between residence and adherence. Marital status was found to have no association with adherence in six studies, with a single study report that married patients were more adherent than those not married (Tsai et al., 2018). Many more variables were also measured in the reviewed studies, but far fewer times including employment/income, religion and tobacco/alcohol use, all of which tended to show no significant association with adherence.

Treatment characteristics

Evidence from the old reviews consistently suggested that increased dose, increased time on treatment and the presence of side-effects were associated with poorer adherence. However, evidence from this new review is less confirmatory of these associations. Seven new studies were found examining dose and adherence, most finding no significant association and two reporting that taking one dose per day (Geissler et al., 2017) or having no decreases in dose (Phuar et al., 2020) was associated with improved adherence. Several more studies were also carried out which looked at treatment duration, the evidence from these is contradictory. Eight showed no significant association between time since TKI initiation and adherence; and six studies suggested that longer time on TKI treatment was associated with poorer adherence (Clark et al., 2020; Phuar et al., 2020; Geissler et al., 2017; Rychter et al., 2017; Cantú-Rodríguez et al., 2015; Hosoya et al., 2015). Three studies agreed with old review findings that increased adverse events (Mulu-Fentie et al., 2016) or symptom burden (Unnikrishnan et al., 2016) were associated with worse adherence or a lack of side effects associated with high adherence (Geissler et al., 2020); whereas nine of the total twelve studies reported no significant association between adherence and side-effects, or adverse events.

Studies comparing different second generation TKIs have grown in number since old reviews, which identified only two studies. However, research investigating the impact of TKI type on adherence shows differing findings in this new review. Six studies showed no significant association between TKI type and adherence; some carrying out multiple comparisons between different drugs. However, one of these studies, and nine more, found a significant association between aspects of TKI type and adherence. Four suggested that those on second line TKIs, usually nilotinib or dasatinib, were more likely to be adherent (Phuar et al., 2020; Maeda et al., 2019; Maeda et al., 2017; Anderson et al., 2015) whereas two found that taking a second generation TKI (Clark et al., 2020; Boons et al., 2018) or third line of treatment (Leader et al., 2018^a) was associated with non-adherence. The remaining studies had a slightly different focus. Smith et al (2016) reported a significantly higher adherence in

those taking nilotinib compared to those on dasatinib, whilst Geissler et al (2017) found that TKI type was strongly correlated to number of doses, with a lower number of doses, i.e. imatinib or dasatinib, (as opposed to nilotinib) being significantly associated with improved adherence. Finally, one study examined generic imatinib against brand imatinib reporting those initiated on generic imatinib had significantly better adherence than those started on brand imatinib, a finding the authors related to lower out of pocket costs incurred by the patient in this USA based research (Cole et al., 2019).

Modifiable factors

Patient experience

The previous section described findings from studies examining fixed variables in relation to adherence such as gender and treatment type. Evidence regarding these associations is increasingly contradictory and less clear, and the characteristics themselves are not amenable to change. The following section examines modifiable variables, which often relate to patient experience and may be amenable to change, to improve adherence or other aspects of care.

Quality of life

Since the old reviews, research investigating aspects of patient QOL and experience, and their relationship with adherence in CML, has grown and the following sections explore this. An overview of the association between QOL and CML is given here, with most studies reporting a detrimental impact of CML on aspects of QOL. Buzaglo et al (2017) found that 45% of patients were at high risk of depression and Boons et al (2018) found that 72% of their sample were “somewhat concerned” about their CML. Studies in this new review also found that the experience of CML could lead to changes in daily life, mental health and household finances (Buzaglo et al 2017; Yanamandra et al., 2017). In the Yanamandra et al study (2017) 22% and 16% of their sample reported moderate and significant (respectively) change to these aspects of daily life. Such changes could include “feeling too tired to do the things you need or want to do”, “worrying about the future and what lies ahead”, and problems “thinking clearly” (Buzaglo et al., 2017). Maeda et al (2017; 2019) examined second generation TKIs and QOL, concluding that QOL was significantly better for those on nilotinib 2nd line, than those on 1st line imatinib.

Most studies suggested that aspects of poorer QOL were associated with worse adherence (Sacha et al., 2017; Unnikrishnan et al., 2016). Physical symptoms in the QOL measure used by Sacha et al (2017) reflected TKI side-effects (e.g. appetite loss, diarrhoea) and this study showed a significant association between poorer QOL and poorer adherence. Unnikrishnan et al (2016) also found that non-adherence was significantly associated with increased symptom burden, using their CML-specific QOL measure, and Geissler et al (2017) reported that those who felt their side effects were

well managed were significantly more likely to be highly adherent. Those with no previous history of depression were significantly more likely to be adherent in Kapoor et al's study (2015). Whilst Kekäle et al (2015) found a significant association between higher number of adverse drug reactions and poorer quality of life, there was no significant relationship with adherence; however the authors suggest this was due to side effects being equally distributed among the high, medium and low adherence groups. Finally, in contrast, Boons et al (2018) reported no association between level of disease concern and adherence.

Treatment satisfaction

Two studies measured treatment satisfaction in relation to adherence. Sacha et al (2017) investigated QOL and adherence in those prescribed nilotinib as second- or third-line treatment. Nilotinib, like other TKIs comes with a side effect profile, and unlike dasatinib and imatinib, is taken twice daily 12 hours apart, and on an empty stomach. Despite this, the authors found that satisfaction with medical care was high and there was no significant association between this and adherence. 87% of patients in the Boons et al (2018) study were satisfied with the disease and treatment information they received, mostly from their physician and the internet, however this level of satisfaction was not significantly associated with adherence.

Reasons for non-adherence

Studies which explored the reasons behind non-adherence generally fell into the categories of intentional and unintentional adherence as described by Eliasson et al (2011), and are included in this section as they represent areas of behaviour which may be amenable to change by practitioners and therefore modifiable. Most patients in studies by Hosoya et al (2015), Rychter et al (2017) and Boons et al (2018), described their non-adherence as unintentional, often due to forgetting to take their medication. However, Mulu Fentie et al (2019) found that forgetfulness was among the least common reasons for non-adherence in their study, and intentional non-adherence due to adverse effects the most common. Similarly, Andrade et al (2019) found that associations with unintentional reasons were mostly not significant, whilst intentional reasons for non-adherence, including abandoning treatment without justification and disinterest in outpatient appointments, were significantly associated with worse adherence. Okumura et al (2015) found that both unintentional (forgetting) and intentional (adverse effects) were common reasons given by those at high risk of non-adherence. Sixty percent of the sample in the Boons et al (2018) study claimed they were not concerned about a missed dose.

Side-effects, or adverse events, were frequently related to intentional non-adherence (Andrade et al., 2019; Mulu Fentie et al., 2019; Rychter et al., 2017). Hosoya et al (2015) found that the risk of

non-adherence was greater in those experiencing diarrhoea, nausea and oedema, whereas muscular pain was more common in those who adhered. This relationship between side effects and intentional non-adherence is interesting as most of the studies described earlier in this new review, which measured side-effects and adherence, found no association between the two. The apparent contradiction in findings regarding the association between side-effects and adherence in this new review, may lie in the way adherence and side-effects were measured, some of the studies described here perhaps looking in more detail at the two variables than those described in the 'treatment characteristics' section.

Social support and coping

As discussed previously in this new review (patient characteristics), marital status was found by most studies to have no significant association with adherence. However, studies examining the broader concept of social support were mostly consistent in their finding that this was associated with improved adherence, suggesting that marital status may not be a good indicator of social support. Living with family or a partner (Geissler et al., 2017; Sacha et al., 2017) was found to be significantly associated with improved adherence and Leader et al (2018^a) found that living alone as well as lack of membership of a CML patient support group, were significantly associated with reduced adherence. Sacha et al (2017) concluded that despite most patients being categorised 'highly adherent' at the end of their follow up period (which was explained by the Hawthorn effect) this was not the case at the beginning of the study, when fewer of those living alone had high adherence compared to those living with family.

Relationship with physician

Seven studies explored factors related to the patient-physician relationship, compared to only two in the old reviews. Kapoor et al (2015) found no association between adherence and level of physician/patient interaction. However, in the study by Geissler et al (2017) 91% of the sample reported that their doctor was "approachable to discuss the challenges of taking CML medication", and these patients were significantly more likely to be in the highly adherent group. The authors also found that those who felt their side effects were well managed were more likely to have improved adherence (Geissler et al., 2017). Sacha et al (2017) found that patients and physicians had good agreement on their MMAS adherence scores, whereas Yanamandra et al (2017) found that physicians greatly over-rated patients' MMAS measured adherence which the authors related to a lack of time in outpatient clinics. Leader et al (2018^a) also found physician rated visual analogue score of patient adherence to be less reliable than the patient assessed BAASIS score when compared to MEMS. An over estimation of adherence by physicians is supported by other studies

suggesting clinic appointments concentrate on treatment decisions rather than other concerns such as adherence. This is reflected in reports that a third of patients felt excluded from shared decision-making in clinics in the study by Yanamandra et al (2017). Also, in the study by Boons et al (2018), of the 60% of patients reporting they were not concerned about missing their medication, some did not discuss missing doses with their doctor or only discussed this if it “came to matter” in their appointment. Interestingly, a study of coping strategies by Hefner, Csef and Kunzmann (2017) found that the most frequent single item from their questionnaire was that patients who coped successfully put “trust in doctors” and would “follow doctor’s orders accurately”; although this was not reflected in the relatively high percentage of non-adherent patients in their sample. In Rychter et al’s (2017) study, patients were also found to over-estimate their adherence, with 69.4% of patients who reported some non-adherence during the study period also reporting they “always” followed doctors instructions. This suggests that the way patients present themselves to researchers and physicians may not reflect how they adhere in practice.

Knowledge and information

Six studies investigated a connection between self-reported level of satisfaction of/with knowledge and information about disease/treatment, and adherence, a topic not found in the old reviews. The proportion of those who reported they would miss medication due to a lack of disease and treatment information was significantly greater in non-adherent, than adherent patients in the Tsai et al (2018) study. The Geissler et al (2017) study had comparable findings; reporting that a higher level of satisfaction with information provided by doctors was significantly associated with higher adherence. In contrast, the same study also reported that being informed about the risks of non-adherence had no significant association with adherence (Geissler et al., 2017). Kapoor et al (2015) also found that level of patient knowledge about disease and medicine, in addition to attendance at education sessions were not significantly related to adherence. Similarly, Boons et al (2018) found no significant relationship between non adherence and patient reported satisfaction with information, sufficient education about TKI use or the need for information, and Unnikrishnan et al (2016) found none between adherence and awareness of diagnosis and treatment. Finally, inadequate drug information was found to be one of the least common reasons for non-adherence in the study by Mulu Fentie et al (2019). It is possible the variations were due to different methods used to measure the level or, satisfaction with, knowledge and information.

Study findings reporting on the level of patient knowledge varied. Interestingly, the Boons et al (2018) study also reported that despite the majority of their sample feeling satisfied with information received (mostly from their physician or the internet), 92% also reported a need for more information, particularly around side effects, the disease, TKI effects, quality of life and

instructions for TKI use. Rychter et al (2017) found 93.6% of their sample reported receiving adequate information about medication adherence. However, in the study by Unnikrishnan et al (2016) the level of diagnosis and treatment awareness was found to be poor, with $\leq 30\%$ being “fully aware”, although this did not predict adherence. Yanamandra et al (2017) reported that just over half their sample had very little or no knowledge of CML or TKI therapy, which the authors considered was due to time pressure on physicians in outpatient’s appointments. This was concerning as 91% of those with ‘some’ or ‘more’ knowledge reported having received this from their physician.

Adherence interventions

This last section describes a further area of research concerned with interventions to promote adherence, which has progressed significantly since the old reviews with eight studies identified. All the interventions were hospital based, and were pharmacy and/or nurse led, and most used multiple methods to improve adherence. For example, Kekäle et al (2016) ran a patient education programme which included IT technologies such as video recordings and text reminders, as well as face to face nurse counselling sessions offering education and psychosocial support. Other interventions included pharmacy monitored medication diary (Santoleri et al., 2019), adherence aids such as blister pack, the provision of i-pads containing educational material (Tan et al., 2020), and behavioural change techniques, such as motivational interviewing (Leader et al 2018^b).

All studies showed that adherence had significantly improved post intervention, implying these multi-method interventions were generally effective. However, comparison between studies was difficult due to differing methodologies. Most had a control group which, when described, was ‘usual’ or ‘standard’ care; and two used a ‘before’ and ‘after’ measurement from within the same sample (Leader et al., 2018^b; and Santeroli et al., 2019). Adherence measurement methods varied. Four studies used MPR and others used patient questionnaires such as the MMAS and BMQ, with one using MEMS. Study periods and follow up also varied and were not always explicit. Interestingly, the study by Tan et al (2020) found that despite a significant increase in the proportion of adherent patients post intervention at the end of study period 6-month point, there was no significant difference in adherence between the intervention and control groups at the 12-month point, the authors suggesting that for an intervention to be effective, it needs to be ongoing (Tan et al., 2020). However, Leader et al (2018^b) reported no decrease in adherence 90 days post intervention (Leader et al., 2018^b).

Despite widespread effectiveness, outcome measures also differed. Some studies measured disease response as a study result (Tan et al., 2020; Moulin et al., 2017; Lam and Cheung, 2016). Moulin et al

(2017) and Tan et al (2020), for example, reported a significantly greater proportion of patients achieving MMR in their intervention groups, and Lam and Cheung (2016) found a larger proportion of non-adherent patients failed to achieve CCyR than adherent patients. QOL and symptoms were measured in two studies. Tan et al (2020) found that some of their QOL measures; worry, insomnia and cognitive functioning, were significantly better in the intervention group than the control group 6 months post-intervention, suggesting this was related to reassurance from the pharmacist regarding prognosis and treatment success (Tan et al., 2020). Finally, Moulin et al (2017) reported that in addition to a reduction in non-adherence post-intervention, there was a decrease in the number of symptoms reported by patients.

2.2.4 Discussion

This chapter includes a review of 38 studies published since January 2015, providing an update on old reviews concerned with TKI adherence in CML. It aimed to answer the question: “What factors in contemporary research are associated with adherence to TKI medications in adults with CML?”. One of the main concerns arising from the old reviews was the lack of a gold standard measurement and a definition of adherence cut-off levels, meaning estimates of non-adherence varied (Gater et al., 2012), and comparison between studies was difficult (Noens et al., 2014). Unfortunately, there seems to have been little progress made in this area, and as a result, estimates of non-adherence continue to vary, from 0-55%. Despite three adherence measures becoming the most frequently used in this new review, the MMAS, MPR and PDC, studies lacked consistent cut-off points when defining adherence. Researcher derived questionnaires varied or did not define adherence levels. Although Gater et al (2012) emphasised the importance of a clinically relevant adherence definition, little progress seems to have been made on this, however some studies based definitions of adherence cut off points on well-regarded CML specific studies on response and adherence, rather than only using limits advised by the users or authors of the adherence measure. Findings are more likely to be of relevance to practitioners if the defined level of adherence is associated with an improved clinical outcome known from the literature.

Progress was demonstrated however, in some use of multiple adherence measurement methods since 2011, as advocated by the old reviews in the absence of a gold standard measure (Breccia, Efficace and Alimena, 2011; Gater et al., 2012; Noens et al., 2014). Eight of the thirty eight studies in this new review used multiple methods, with four combining objective and subjective measures.

Regarding the consequences of non-adherence, this new review provided further evidence to support the old reviews finding that increased adherence impacts on disease response, commonly an improved molecular response, with new studies also linking improved adherence to longer

survival. More studies also emerged, still predominantly from the USA, showing an association between increased healthcare costs and non-adherence.

Evidence of an association between adherence and non-modifiable patient and treatment characteristics, has become more equivocal since the old reviews. Associations between adherence and age remain contradictory, continue to be unclear for concomitant medication and comorbidity variables; and the majority of studies now show no association with gender. Some of the studies examining the relationship between finance and adherence showed increased costs to the individual were associated with increased non-adherence, although others were contradictory and suggested factors other than cost may contribute to non-adherence.

New studies investigated other socioeconomic factors, although variables such as education level, residence and marital status showed little, if any, association with adherence. Recent studies also showed either contradictory results, or little evidence of any, association between non-adherence and increased dose, increased time on treatment or side-effects, in contrast to the old review findings. Finally, new studies were carried out on the impact on adherence of second generation TKIs, as suggested by Gater et al (2012) and Noens et al (2014), however most showed little consensus, with over a third finding no association between aspects of second generation TKIs and adherence.

More promisingly, many new studies were identified in this new review were concerned with variables associated with adherence that are potentially modifiable in clinical practice; all of which relate to patient experience. With respect to Gater et al's (2012) appeal for more research exploring the patient experience as a result of their literature review, it was argued that adherence research at that time did not allow an understanding of the patient experience and the individual drivers behind adherence, or the importance of an individualised approach to adherence management (Almeida et al., 2014; Gater et al., 2012; Jabbour et al., 2012^a). Generally, various aspects of quality of life (QOL) were found to be impacted by living with CML, in this new review, and worse adherence could be associated with aspects of poorer QOL. In contrast, while treatment satisfaction was high in two studies, there was a little evidence to suggest an association between this and adherence. The main reasons for non-adherence were found to be the same as those identified by Eliasson et al (2011); unintentional forgetfulness, and intentional avoidance of side-effects. This contradicted other new studies examining adherence and adverse events/side-effects, most of which found no association, perhaps due to a difference in the measurement of side-effects or the focus of the study.

New studies consistently reported an association between aspects of social support and improved adherence, most showing that living with family or a partner was related to improved adherence.

This contrasts with other studies in this new review reporting no relationship between marital status and adherence, suggesting this may not be an accurate measure of social support. This new review also identified several studies examining the patient-physician relationship, although the influence of this on adherence was unclear and measures differed. There was some agreement between physicians and patients on their MMAS adherence score, however physicians could also overestimate patient adherence. Various explanations were offered for this including that clinic appointments may focus on physician-based treatment decisions, perhaps due to pressure on clinic time. This is reflected in reports of patients feeling excluded from decision making, or not informing their doctor about missed doses. Others claimed to follow doctors instructions although the same patients were less adherent than this suggested implying that what patients tell physician may differ from how they actually act. Overall, these factors are concerning as they suggest patients may feel they cannot discuss non-adherence with their physician. Finally, studies included in this new review found mixed levels of disease/treatment knowledge and awareness, and satisfaction with information, among patients. The evidence on whether this could predict adherence was also contradictory, which again may be due to different measures used.

Old review authors described features of optimal adherence interventions and some argued further research was needed into these (Breccia, Efficace and Alimena, 2011; Almeida et al., 2014; Jabbour et al., 2012^a). Eight studies in this new review reported on such interventions. All used combined methods and were hospital based and led by nurses and/ or pharmacists. Although these studies showed the interventions generally had a positive effect on adherence, different outcome and adherence measures were used by the studies, and follow up periods varied or were not stated, making comparison between studies, and overall conclusions difficult. Furthermore, generalisation of findings outside the hospital environment may be limited.

Overall, this new review offers an important update on current knowledge concerning factors associated with adherence to TKIs for patients with CML. Unfortunately, there has been a lack of progress in identifying a gold standard measure of adherence or an agreed adherence definition or cut off levels. However, more studies now use multiple adherence measures, which may enhance their validity. Recent literature questions whether any significant association exists between patient and treatment characteristics, and adherence. Therefore, identifying non-adherence risk groups based such characteristics, e.g. age and time on treatment, may be erroneous. Moreover, such variables are difficult, if not impossible to modify in practice.

An area of research development has been in exploring modifiable aspects of the patient experience, which has enhanced our understanding of how individuals manage their TKI treatment suggesting a multifarious picture of this experience, and highlighting the difficulty of measuring

these complex variables and how they relate to adherence. Qualitative work on this phenomena may deepen our understanding of the dynamics of the patient experience and its relationship with self-management. This would also help identify patient drivers necessary for interventions to be effective.

2.2.5 Strengths and limitations

This new review provides a comprehensive overview of studies relevant to my overarching question regarding factors associated with adherence to TKIs. It updates old reviews and reports on advances in study methods and findings, as well as areas where progress is needed. A narrative review is presented, which used a systematic methodology and presented findings in both tabular and textual format. The search strategy was comprehensive and thorough, and although a second researcher did not check my study selection and data extraction, I discussed this regularly with my supervisors. Multiple, well regarded databases were used to identify publications and produced a large number of relevant studies. Included studies originated from around the world meaning various cultural/systematic factors may have effected findings and limited generalisability outside that country. However, it ensured the review incorporated health infrastructure-specific factors. Grey literature, conference abstracts and non-English language papers were excluded due to time-constraints. Some terms were omitted from the search, in order to focus on key issues, but these often described a different phenomenon to adherence (e.g. “persistency”, “discontinuation”) so would not have been of interest.

An appraisal tool was used to assess the quality of included studies, as the quality of the studies themselves may limit the generalisability of findings. Overall, the quality of the non-randomised studies was good and they were well reported. However, most studies, of a quantitative descriptive design, lacked some methodological detail, particularly in reporting whether their sample was representative of the population under study (inclusion/exclusion criteria etc.) and response rate, which may limit their generalisability. Finally, there may be some lack of depth in my own critical analysis, for example in the assessment of statistical analysis and identification of possible bias, as I had limited expertise in some areas, however my review adequately answers the review question and covers a large number of studies.

2.2.6 Application to practice

The new review findings demonstrate that there are no specific patient or treatment characteristics clearly associated with TKI adherence in CML. Therefore, to attempt to identify a group “at risk” of non-adherence would be inappropriate. Furthermore, these factors are generally not modifiable by

people providing patient care. In contrast, factors relating to patient experience are modifiable and intervention studies have shown that combining methods such as education and psychosocial support are effective in improving adherence. However, if considering the implementation of similar interventions in practice, careful consideration of the context of this practice area may be important to ensure its success.

2.2.7 Future research

Studies of patient experience in this new review used patient reported outcome measures, however such instruments are restricted to pre-determined, closed questions, so are unable to incorporate the detail of an individual's experience of managing their disease. Understanding people's motivations and behaviours around their self-management can enhance our understanding of why people may be non-adherent, and helps understand the context within which adherence interventions may be delivered. This review suggests many factors may impact on patient experience and self-management. Qualitative research offers a more in-depth investigation of experience and motivations involved in self-management. Therefore, a synthesis of qualitative studies examining TKI adherence and the CML patient experience would be of value. To this end, the following chapter addresses this deficit, by conducting a qualitative synthesis of studies examining the CML experience.

Chapter 3 Qualitative synthesis

The literature review chapter highlighted the need for a review of qualitative work exploring the experiences of living with, and managing CML. Articles included in the literature review often measured an association between fixed variables and adherence, such as age and gender, which did little to explain adherence behaviour. However, some of the included literature was also concerned with aspects of the patient experience, such as social support and Dr-patient relationships, which in addition to offering more description of this experience, were potentially modifiable in practice. This literature suggested adherence was not an isolated issue but part of a complex, interwoven experience. The value of a synthesis of the qualitative literature would be to complement and move beyond the literature review findings, in order to understand the complexity of the experience of living with and managing CML from the patient's perspective. This chapter describes the process and findings of a qualitative synthesis of studies concerned with the CML experience. It aims to enhance our understanding by exploring patient behaviours and coping from their own perspective and in their own words. This in turn can facilitate an understanding of how contextual factors may influence disease self-management and help create a topic guide for patient and practitioner interviews.

3.1 Qualitative synthesis and its methods

Qualitative syntheses go beyond a simple literature review of qualitative studies, by using a method of analysis that combines study findings into an overall interpretation (Britten et al., 2002; Pope and Mays 2006). Debate exists about their value as some argue that the individual methodological approaches and study interpretations may be lost in the synthesis (Thorne, 2017; Thomas and Harden, 2008; Pope and Mays, 2006; Booth 2001). However, qualitative syntheses can be used to enhance the findings from individual studies, identify gaps in knowledge, improve primary research quality and facilitate investigation of similarities and differences between samples and populations (Toye et al., 2013; Paterson, 2012; Flemming, 2007).

Unlike quantitative synthesis methodology, there appears to be much discussion around qualitative synthesis methods, suggesting the need to justify one's approach. Since its origin in the late 1980s, there are now over thirty qualitative synthesis methods described in the literature (Noyes et al., 2018^a; Paterson, 2012), with the most influential being meta-ethnography (Noblit and Hare, 1988) and meta-study, both of which being integrative approaches to synthesis (Hannes and Macaitis, 2012; Paterson, 2012; Barnett-Page and Thomas, 2009). Several other models have been developed during this time and more recently the Cochrane collaboration has accepted the value of qualitative synthesis in enhancing evidence for decision making in health care (Noyes et al., 2018^a). Paterson

(2012) and Booth et al (2016) have developed guidance to facilitate selection of the most appropriate methods, and authors stress the importance of careful selection which is considered crucial (Pope and Mays, 2006; Barnett-Page and Thomas, 2009). Based on this guidance and other literature, and after considering my research question, epistemology, nature of researcher/resources, data, and key reference material, thematic synthesis was selected for use in this thesis, as discussed below.

In terms of underlying epistemology and the synthesis question, I wanted to discover what was known about CML patients' feelings, behaviour, and experience of their disease, to complement and further the findings from my narrative literature review. The synthesis question became: "*what are the experiences of adults taking long term TKI medication for chronic phase CML?*". This represents a broad, "negotiable" and "emerging" question rather than it being "fixed" or focussed (Booth et al., 2016), which is suited to an interpretive or iterative approach. This approach is characterised by the notion that the reality of the CML experience is how the individual describes it and involves the building of concepts from study findings which are linked together to form theory (Dixon-Woods et al., 2006, 2005). It contrasts to an approach answering a more focused question, which may be more suited to aggregative or integrative reviews (Dixon-Woods et al., 2006; Fisher et al., 2006).

Methods involving a more interpretive approach include meta-study, grounded theory and meta-ethnography (Paterson, 2012). However, despite the interpretivist nature of the synthesis question, the final aim of the study is pragmatic; to provide evidence relevant to practitioners that could be used to improve the care and support of CML patients. Thematic synthesis provides a solution to this issue by representing a different epistemology; the realist approach (Paterson 2012; Booth et al., 2016) which fits the overall study aim. Paterson (2012) describes this realist approach as emphasising the "possibility for research to adequately represent an external reality", comparable to the idea of Hammersley's (1992) "subtle realism" (see methodology chapter), which accepts both that there is a shared reality outside of us, but that this reality can only be known through the minds and perspectives of individuals.

Next, I considered the nature of the researcher (myself) and the research team, available resources, and the expertise required for certain methods (Paterson et al., 2012; Booth et al., 2016). Some methods, such as meta-aggregation and grounded theory, require more specialist knowledge than more structured approaches such as framework synthesis and critical interpretive synthesis (Paterson et al., 2012; Booth et al., 2016). As a PhD student, with responsibility for the synthesis and only minor input from a senior qualitative researcher, I was aware that although I had skills in literature searching, I was a novice in qualitative synthesis. Although the methods of thematic synthesis are regarded as not entirely clear (Thomas and Harden, 2008), I had attended training on

thematic analysis in preparation for my patient interview analysis and felt that this would provide sufficient knowledge, in addition to relevant reading, to undertake the review. Regarding my own philosophical stance, this is pragmatic, with practical, problem solving aspects, originating from my NHS nursing background; and well suited to the realist approach encompassed by thematic synthesis. Resource requirements vary by study size and complexity (Paterson 2012; Booth et al., 2016), with little required for this synthesis, as the initial search identified few studies to include. Regarding time and personnel, as the synthesis is part of my PhD, I planned to conduct the bulk of the work myself, with minimal support from a senior researcher (noted above) and regular input from my supervisors, which seemed appropriate. Furthermore, although little is written on the resource requirements of thematic syntheses, this is a well-used method (Hannes and Macaitis, 2012), suggesting it is not overly resource intensive.

Further matters for consideration include comparability of studies in the synthesis, type of data, frequency of methods used, and recommendations from colleagues (Saini and Shlonsky 2012; Booth et al., 2016). In this synthesis from the initial search, it appeared that although heterogeneity existed, the papers used similar methods and produced similar, potentially comparable data. Booth et al (2016) elaborate on this and advise using a method which suits the number of studies to be included, and also describes methods which suit “thin” or “thick” data in terms of context, and “rich” or “poor” data in terms of theory. The included studies ranged in “thickness” of contextual detail and “richness” of theory. Little is documented on how many studies are required for meaningful thematic synthesis, although Booth et al (2016) report it can accommodate a large number. Thematic synthesis can also manage “thin”, “poor” data unlike other approaches which require “rich”, “thick” data such as meta-interpretation and grounded theory (Booth et al., 2016). Although it is advised not to accept methods solely due to them being familiar to colleagues (Booth et al., 2016), I also consulted an expert colleague from the Cochrane Qualitative and Implementation Methods Group who advised the use of thematic synthesis.

Work providing a reference guide for the synthesis process include an example by Thomas and Harden (2008), Braun and Clarke’s (2013) guidance on thematic analysis, and also other thematic synthesis papers concentrating on patient experience (Usher-Smith et al., 2017; Dohnhammar, Reeve and Walley, 2016; Ogilvie et al., 2012). Thomas and Harden’s work (Thomas and Harden, 2008; Thomas et al., 2004) on thematic synthesis, influenced by Braun and Clarke’s (2013) qualitative analysis techniques, are widely recommended by authors as key reference material (Flemming 2007; Barnett-Page and Thomas 2009; Paterson 2012; Booth et al., 2016). Thematic synthesis involves identifying analytical themes across included studies following a descriptive coding process, these themes reflecting relationships and disparities between the data (Barnett-

Page and Thomas 2009; Paterson 2012). Thomas and Harden (2008) criticise thematic synthesis for lacking clear guidance and present an example of the approach used in their study. Dixon-Woods et al (2005) also note that guidance is lacking on the level of interpretation involved, or whether the thematic synthesis is purely a descriptive summary. This synthesis aims to surpass study description and summary and interpret the synthesised data. Each step of the process will now be described, along with the results.

3.2 Methodology

3.2.1 Search strategy

Little guidance exists on strategies for conducting a qualitative synthesis search, although “conceptual saturation” is considered more applicable than identifying all relevant studies as is common in quantitative meta-analysis to support statistical significance (Thomas and Harden 2008). Some of the reference studies I used adopted more structured searches, similar to those in quantitative reviews, such as use of the PICO criteria (Ogilvie et al., 2012; Usher- Smith et al., 2017). Like Dohnhammar et al (2016), I decided not to apply formal criteria, due to my wide-reaching, multifaceted question. In practice, similar to Thomas and Harden (2008), my search strategy did not differ much from that of the quantitative literature review, in that inclusion/exclusion criteria, phenomena of interest, context and study types were defined in advance.

To optimise the search, I sought advice from an Information Service Manager at the University of York. Based on this, I began with a small, specific search on: ‘chronic myeloid leukaemia’, ‘patient satisfaction’ and ‘qualitative’, followed by a citation search on each of the studies identified in order to widen the search. Five databases were examined in this way, with alerts set up to capture all articles published over the duration of my thesis. The final strategy with inclusion/exclusion criteria is shown below, along with the number of studies retrieved at each stage of the process (Figure 5)

Search terms and databases

Search terms:

- Chronic myeloid leukaemia *or* Chronic myeloid leukemia *or* Leukaemia myelogenous chronic BCR-ABL positive
- and*
- Patient satisfaction *or* patient experience *or* qualitative research

Databases:

- MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index (Web of Science), Google Scholar, EThOS

Citation search:

- Scopus: to carry out a reference list search on included studies.

Inclusion and exclusion criteria

Inclusion

Participants:

- Adults aged 18 and over
- Male and female
- Diagnosis of CML
- In chronic phase when study conducted
- On long term TKI medication (i.e. lifetime medication)

Phenomena of interest:

- Experiences of CML and taking TKI tablets

Context:

- An outpatient setting (i.e. treatment taken outside the hospital setting – usually at home).
- Any geographical location.

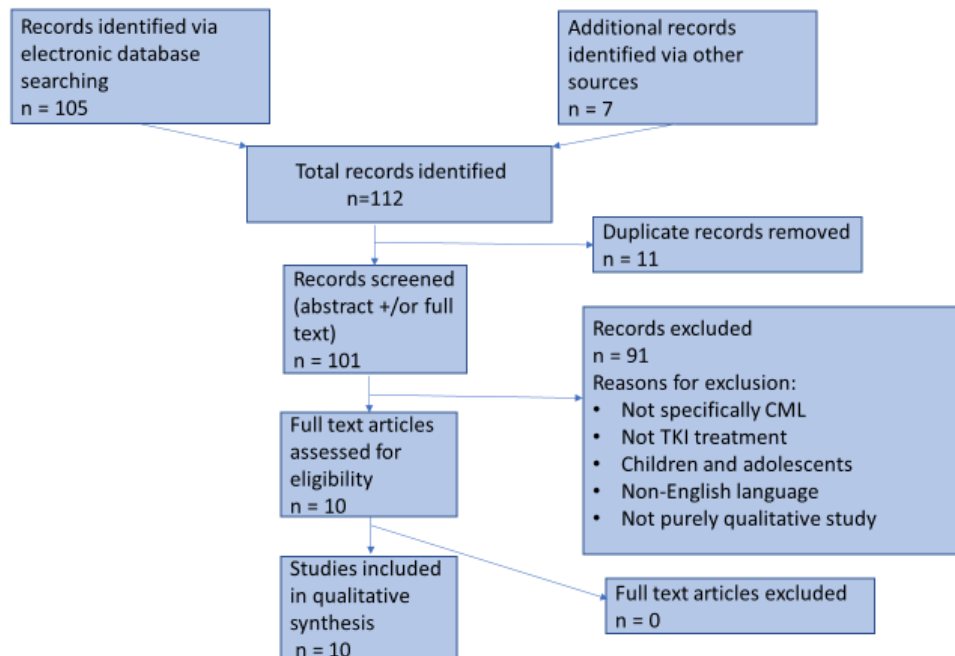
Types of studies:

- Qualitative methods only.

Exclusion criteria:

- Studies of children/adolescents
- Clinical trials or other quantitative study
- Systematic reviews
- Studies not written in the English language
- Studies focusing on end of life care

Figure 5 Screening process and identification of eligible studies (thematic synthesis)



3.2.2 Summarising the studies

As a first step in thematic synthesis (Thomas and Harden 2008), each paper was read and re-read for familiarity, before summarising key points (see appendix 2 for an example of a study summary). This provided an overview for use during the analytical process. It was difficult to determine precisely which data to include in the summary, so I based this on Cochrane guidance (Noyes et al 2018^b), as well as the collated reference studies (Ogilvie et al., 2012; Dohnhammar et al., 2016; Usher-Smith et al., 2017). This summary is shown below in table 2.

Table 2: Summary of included studies: thematic synthesis

Author/year	Population/country	Participants (N, age, sex)	Research question	Data collection	Research approach/analysis
Eliasson et al 2011	CML patients attending hospital, UK	N=21; Age 33-70 Male 11, Female 10	To explore the experience of CML patients of taking (or not) imatinib as prescribed	In-depth unstructured interviews	Constant comparison
Guilhot et al 2013	CML patients in clinical centres and online communities, Brazil, France, Germany, Russia, Spain	N=50; Age 21-80 Sex not reported	To assess effects of diagnosis and treatment on patients with CML, with recommendations for Health Care Professionals to better support patients	In-depth, semi-structured interviews with patients/relatives; diary, photo journal, debriefing interview (Brazil, France only)	Ethnography
Chen et al 2014	CML patients attending oncology outpatient clinic, Southern Taiwan	N=42; Age 20-80 Male 23, Female 19	To explore CML patient experiences of treatment with imatinib, and understand perceptions, attitudes and concerns influencing adherence	Semi-structured interviews	Constant comparison; theme saturation
Wu et al 2015	CML patients and HCPs at a specialist cancer centre, Australia	N=16; Age 26-71 Male 9, Female 7 Practitioners: N=10 (nurses, haematologists, pharmacists)	To explore and compare patient experiences with HCP perceptions of imatinib	Semi-structured interviews	Interpretative phenomenological analysis
Graffigna et al 2017	CML patients in 22 onco-haematological centres, Italy	N=158 Characteristics not reported	To reconstruct the subjective meaning of CML and explore the psychological impact of suspending therapy	Narrative diaries	Narrative inquiry; lexicography analysis and “purely qualitative analysis” of narratives by hand.
Lim, Eng and Chan, 2017	CML patients at a tertiary care centre, Northern Malaysia	N=13; Age 47.8 (mean) Male 8, Female 5	To explore patients’ understanding and challenges in taking imatinib and nilotinib	Semi-structured interviews; questionnaire	Content analysis
Mortensen and Mourek 2017	CML patients treated at seven hospitals across Denmark	N=20; Age 36-75 Male 8, Female 11	To investigate motivations and barriers to adherence	Semi-structured individual interview and focus groups	Inductive content analysis
Tan et al 2017	CML patients attending haematology clinics in two medical centres, Malaysia	N=18; Age 26-67 Male 9, Female 9	To explore non-adherence reasons and medication related issues	Semi-structured interview	Thematic analysis
Bolarinwa et al 2018	CML patients attending the only hospital providing free imatinib, Nigeria	N=20; Age 25–56 Male 10, Female 10	To evaluate delayed diagnosis, health-seeking, medication and other challenges faced by people living with CML on imatinib	In-depth semi-structured interviews	Grounded theory (until saturation); content analysis of themes
Boons et al 2018	CML advocacy group patients, treated at 9 hospitals, Holland	N=13; Age 27-73 Male 5, Female 8	To understand reasons for non-adherence and patient need for information and communication	Semi-structured interviews; questionnaire	Mixed methods; qualitative thematic framework analysis

3.2.3 Quality Appraisal

Several methods are available to appraise the quality of qualitative studies, with little guidance on choice (Thomas and Harden 2008). Santiago-Delefosse et al (2016) recently reviewed 58 quality assessment guidelines, developing a measure of 12 quality criteria. However, this instrument is not as user-friendly as other tools, such as CASP (CASP-UK 2018) and the measure devised by Hawker et al (2002), and not as widely cited. Advice was, however, forthcoming from an expert colleague (Cochrane Qualitative and Implementation Methods Group), who suggested use of Hawker et al's (2002) instrument. Furthermore, Noyes et al (2018^b) suggested features to be considered when selecting a tool, some of which are included in the Hawker et al (2002) tool; it can accommodate qualitative studies with differing methodology and helpfully does not include criteria for mixed methods or quantitative studies, which would not be relevant to this synthesis. The format is simple to follow asking the researcher unambiguous questions on the most significant aspects of the study i.e. methodology, analysis, findings. It has now been widely cited in other papers, and overall seemed a suitable choice for use in this synthesis.

Each study was examined using this tool (Hawker et al., 2002) and allocated "poor", "fair" and "good" gradings, which were checked by a second, senior researcher and discussed until agreement was reached. The results are shown as shown in Table 3.

Table 3 Quality appraisal of included articles using Hawker et al (2002): thematic synthesis

Author/ year	Abstract/ title	Intro./ aims	Methods/ data	Sampling	Data analysis	Ethics/ bias	Findings	Transfer- ability/ generalis- ability	Implication/ usefulness
Eliasson et al 2011	Good	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair
Guilhot et al 2013	Good	Fair	Good	Fair	Fair	Fair	Good	Fair	Fair
Chen et al 2014	Good	Fair	Fair	Fair	Poor	Fair	Fair	Fair	Fair
Wu et al 2015	Fair	Good	Fair	Fair	Fair	Fair	Fair	Fair	Good
Graffigna et al 2017	Fair	Fair	Fair	Poor	Fair	Poor	Fair	Poor	Fair
Lim, Eng and Chan, 2017	Good	Good	Good	Fair	Poor	Fair	Fair	Good	Good
Mortensen and Mourek 2017	Good	Good	Good	Fair	Fair	Fair	Good	Fair	Good
Tan et al 2017	Good	Good	Good	Fair	Fair	Fair	Good	Fair	Good
Bolarinwa et al 2018	Fair	Fair	Fair	Fair	Poor	Fair	Good	Fair	Fair
Boons et al 2018	Fair	Fair	Fair	Fair	Poor	Fair	Good	Fair	Good

3.2.4 Results of quality appraisal

Quality was assessed from the published papers based on each study, meaning some of the weaknesses identified might in fact have been simple omissions from the paper, for example, due to journal word limits. Nevertheless, the publication is all the evidence available for quality assessment. A concern throughout the studies was a lack of thorough methodology reporting, with several studies failing to report the relationship between the research team and participants, sampling and inclusion/exclusion criteria, and the characteristics of those who dropped out. A further concern was that several studies that reportedly used a theoretical framework neglected to explain how this was applied during data collection and analysis. For example, Wu et al (2015) used interpretive phenomenological analysis (IPA) in their study, but did not describe how features of this approach were implemented, including how the researchers own conceptions contributed to the findings, or how the interpretive part of the analysis was carried out. Some studies mentioned methods used in theoretical approaches but did not explain how these were carried out, for example Eliasson et al (2011), Chen et al (2014) and Lim, Eng and Chan (2017) all report reaching a point of 'data saturation' but did not explain how this was defined and used in the data collection/analysis. In contrast, the strength of the ten studies appeared to be in their reporting of findings. Although this varied from a more descriptive account (Chen et al., 2014; Bolarinwa et al., 2018) to a conceptual account of the patient journey (Guilhot et al., 2013; Graffigna et al., 2017), data presented and findings were generally consistent, quotations were used to illustrate findings, and themes were clearly presented.

3.2.5 Decision to include or exclude

Based on recent Cochrane guidance (Noyes et al 2018^b) and comparable qualitative syntheses (Thomas and Harden 2008; Ogilvie et al., 2012; Dohnhammar et al., 2016; Usher-Smith et al., 2017), all ten studies identified in the search were included, for reasons now explained. Noyes et al (2018^b) suggest that including studies with limited methodological quality may not contribute substantially to the synthesis, and only including studies based on their relevance to the synthesis question in terms of context or "conceptual robustness" may enhance findings that could be lost if all studies are included. However, the authors also recommend considering the research question and number of studies. I decided to utilise all ten studies, as excluding any would risk losing an interesting perspective, that could be important in such a broad question. Furthermore, despite some methodological concerns, the ten study findings were well-presented. Each had a slightly different approach in its research question and all came from different countries, perspectives which could be lost if studies were excluded. Thomas and Harden (2008) also advise that quality assessment should

prevent the creation of unsound theories based on included study findings. Consequently, Ogilvie et al (2012) and Dohnhammar et al (2016) reported use of their assessments to enrich data synthesis and analysis, rather than exclude studies, an approach I also adopted.

3.2.6 Data extraction

In their thematic synthesis, Thomas and Harden (2008) considered any data reported in the results sections of the papers they selected as study findings, for use in the analysis. This included participants' quotes, researcher summaries and analytical concepts. Noyes et al (2018^b) go beyond this, advising that findings may be located outside of these sections, including for example, the researcher's theoretical interpretations in the discussion. After initial reading and re-reading of included studies, my feeling was that all the findings were contained within the results sections of the papers, so I initially extracted and coded these data. However, as part of an iterative approach, after a further re-read of studies and summaries and checking coding against findings, I was aware that I may not have fully captured each paper's 'message' or 'context' by just using the results sections. For example, Eliasson et al (2011) combine three findings from patient/practitioner interviews in their discussion, which I coded separately based on the results section:

“The interview data thus suggest that HCPs tend to focus on giving patients positive feedback regarding clinical response, while patients seem to rely on the clinician to let them know if their response is being negatively affected by their non-adherence (of which the clinician was not aware). At the same time, very few patients would raise the issue of non- adherence with the HCPs involved in their care” (Eliasson et al., 2011. p.630)

By linking these findings in their discussion, however, the researchers suggest a concept that the patient and practitioner create an assumption together that the patient is managing their medication well. From this, the authors conclude that practitioners should have more “open, non-judgmental” conversations with patients about the possible effects of non-adherence (Eliasson et al 2011). By using this discussion in the extracted data, it can then be coded and used in this synthesis as a standalone concept, in addition to the three separate pieces of information about practitioners giving positive feedback, patients relying on practitioners to tell them about their response, and patients not tending to tell practitioners about non-adherence. It means the researcher's interpretation is thus included and keeps the meaning of the study within the synthesis. A further concern was that several of the studies' discussion sections presented suggested improvements to clinical practice. As one of the aims of this study was to generate findings that could inform and

impact on practice, I went back to each paper and extracted and coded data from the discussion sections, including summaries and interpretations of findings, and suggestions for improvements.

3.2.7 Coding

Rather than coding according to an *a priori* framework or theoretical model, coding was derived inductively from the data, reflecting the open-ended synthesis question. To carry this out, complete coding was used, as practiced in thematic analysis (Braun and Clarke 2013) and followed by others (Thomas and Harden 2008; Dohnhammar et al., 2016). Coded text from the papers included both participant quotes and author interpretations or descriptions of the patient/practitioner data. Meta-ethnography syntheses (Toye et al., 2013; Campbell et al., 2011; Britten et al., 2002) refer to a distinction between the two, citing Schutz's (1962) description of 'first order interpretations', meaning the participant's own words or interpretations, and 'second order interpretations' which is text representing the researchers' interpretations. In meta-ethnography the text of interest is 'second order interpretations', although in this synthesis both patient quotes and researcher interpretations were coded as part of complete coding, so the distinction was less useful. However, it did encourage me to consider the level of interpretation in each paper and how this differed. Some papers offered a more descriptive summary of the data based around participant quotes (Chen et al., 2014; Bolarinwa et al 2018), whereas others presented interpretive text based on their data (Guilhot et al., 2013; Graffigna et al., 2017). The latter raised my concern that the overall interpretation or meaning could be lost in the synthesis, and to minimise this I revisited these papers as part of the re-coding process, as discussed later.

Each paper was coded by hand on the manuscript, with text underlined, code names written in the margins, and code added to a coding frame (a word document) to maintain an organisational system (Braun and Clarke 2013). In essence, codes were named to encapsulate the "meaning and content" of the text (Thomas and Harden 2008). Coding of the first paper revealed that sub-codes were required which were logical, but which still allowed the detail required. For example, '*CML impacts on quality of life*' contained several sub-codes describing this in more detail, such as '*depression*' and '*leisure activities*'. Following hand-written coding, each paper was uploaded to the qualitative software programme NVIVO (versions 11 and 12), with codes and notes electronically replicated within this system. This was an iterative process of revisiting papers and the coding to check content and meaning, as is further described below.

Throughout coding, I referred to the coding frame, which began by coding paper one then labelling the subsequent paper's text under the existing codes or creating new codes. This involved comparing text from one study to the next and considering whether this held the same meaning,

and therefore could be situated under the same code. Thomas and Harden (2008) describe this process as the beginning of synthesising the studies and a ‘translation’ of concepts, a notion originally described by Noblit and Hare (1988) to describe a process of ‘putting together the studies’, where text is examined for comparisons and contrasts (Flemming et al., 2015). For example, the code ‘*patient CML perspective following diagnosis differs*’ contained the sub-code ‘*relief or less fear*’. Both text within the first paper: “*Becoming relaxed with taking imatinib as responding well*” (Eliasson et al., 2011) and the second paper: “*I don’t really worry about it anymore. Of course, you are happy to hear that everything is ok.*” (Guilhot et al., 2013), were placed under this same sub-code as I considered them to hold a similar meaning. This example also demonstrates use of the researcher’s text as well as direct patient quotes.

I coded the first four papers in this way, building up the coding frame and keeping a record of changes and additions after each paper was completed, with new additions added in italics. Figure 6 gives an example from this early coding frame.

Figure 6 Example of early coding 1 (thematic synthesis)

Code: *Patient CML perspective following diagnosis differs*

Sub-codes:

- Good luck
- Lucky
- Value life
- Moving on
- Living with it
- Lees fear/relief
- Not ill
- Fearful
- Satisfied with health status
- *Others worse off*

As coding progressed the frame become increasingly unwieldy, so codes and sub-codes were merged, or more appropriate codes created. In order to decide on which codes/sub-codes could be merged I used NVIVO (versions 11 and 12) which could retrieve all the text from each of the uploaded papers which applied to a chosen code/sub-code, as well as surrounding text to provide context, where required. Consideration was also given to the use of Atlas Ti which although similar to NVIVO in many ways with possibly a slightly simpler function for changing coding, I decided against as it was less well used within the Department. NVivo (versions 11 and 12) was chosen after discussion with my supervisor and others with experience of using this package, as well as IT

specialists. It was the method used by Thomas and Harden (2008); was available to University students free of charge and I was able to test it using the on-line manual before deciding to commit to it.

Some codes were edited to create new codes that more accurately represented the breadth of the data. For example, two sub-codes under the code *'reporting issues to HCP'* were created, as they described instances of patients *not* reporting issues to their HCP, such as *'doesn't want to bother doctor'*, which were different to the other codes which described situations where patients would report issues to their HCP e.g. *'would check with Dr before stopping imatinib'*. A new code was added called *'non-reporting of issues to HCP'* to represent the spectrum of text related to this. Figure 7 gives a further example of this early coding. I also compiled definitions of the more similar codes in order to keep a record to refer to, to ensure consistent coding.

Figure 7 Example of early coding 2 (thematic synthesis)

<p>Abbreviations:</p> <p>HCP: Health Care Professional</p> <p>CAM: Complementary and Alternative Medicine</p>	<p>Codes: Reporting of issues to HCP</p> <p>Sub-codes:</p> <ul style="list-style-type: none"> • Check CAM with HCP • Would check before stopping imatinib • Non-adherence <p>Code: Non-reporting of issues to HCP</p> <p>Sub-codes:</p> <ul style="list-style-type: none"> • Doesn't want to bother Doctor • Non-adherence or changing dosage • Not important <p>Code: Facilitators to patient reporting</p>
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Throughout the coding process, I looked back at my study summaries and compared these to the coding frame. At times I felt I had lost the 'meaning' of some individual papers. For example, Wu et al (2015) suggest an incongruence between patients and professionals in their understanding of adherence which I felt my coded text did not reflect. Accordingly, and as discussed earlier, I re-read all the papers and my study summaries, and coded the discussion sections, as these tended to include more of the authors' interpretation of their data. For example, in Wu et al's (2015) discussion, the text: *"HPs were not always aware of patients' nonadherence. Detection of nonadherence was usually based on patient self-report; however, two patients admitted that they did not report nonadherence"* (Wu et al., 2015), was coded into *'lack of HCP awareness'*, sub-code *'unaware of the scale'* and also *'non-reporting of issues to HCP'*, sub-code *'non-adherence'*. These codes now included the more conceptual idea that the patient and HCP were at odds with each

other, as the HCPs may think the patient is adherent, whilst the patient isn't adherent, but doesn't report this. This process also led to an expansion of text in the code '*possible improvements*' reflecting parts of the discussion that had used the findings to support suggestions for improvements to practice and adding more 'second order interpretations'. Other codes were also enhanced by the coding of discussion sections.

Throughout the iterative process, codes were reviewed, merged, edited and defined, as described. Finally, I employed a repetitive process of going back to the text for each code of interest and considered if it conveyed the same meaning as the other text or whether a new code was needed, until the coding frame was finalised, a process commonly advocated (Barbour 2014; Braun and Clarke 2013; Pope, Ziebland and Mays, 2006). The ultimate frame contained thirty-eight codes, grouped by similarity, under headings such as: '*managing disease and medication*' and '*patient awareness and understanding*' (see appendix 3 thematic synthesis: final coding frame). These headings were not considered themes for analysis, rather they were lists to promote the organisation of codes. Braun and Clarke (2013) describe these as 'overarching headings' to structure codes, but not necessarily for use as analytical themes. Developing analytical themes was the next stage in the process.

3.2.8 Creating analytical themes

In order to develop analytical themes I used a process of examining "similarities and differences" amongst the codes described by Thomas and Harden (2008). Ogilvie et al (2012) and Dohnhammar et al (2016) describe a comparable process. Braun and Clarke (2013) emphasise that theme names should give meaning to the concept described rather than just a descriptive term. For example, I chose to name a sub-theme '*perspective on life is changed*' which tells us that the experience of CML changes people's perspective on life, whereas a sub-theme called '*perspective on life*' would not differentiate between people with CML and anyone else. The final coding frame was examined for patterns across codes which were under five headings: "*Managing disease and medication*", "*HCP advice and communication*", "*Patient awareness and understanding*", "*Quality of life*" and "*Patient perspectives and hopes*" (see appendix 3 thematic synthesis: final coding frame). Codes were considered for similarities across these groups, and NVIVO was used to extract the data assigned to the codes of interest. Upon completion of final editing, ten themes and fifteen sub-themes were created. Codes were added alongside the sub-themes and colour coded by heading to allow me to track-back my coding.

I found going beyond these early descriptive themes to create analytical themes difficult. To facilitate this process, I printed code names onto paper, cut them out and physically moved them

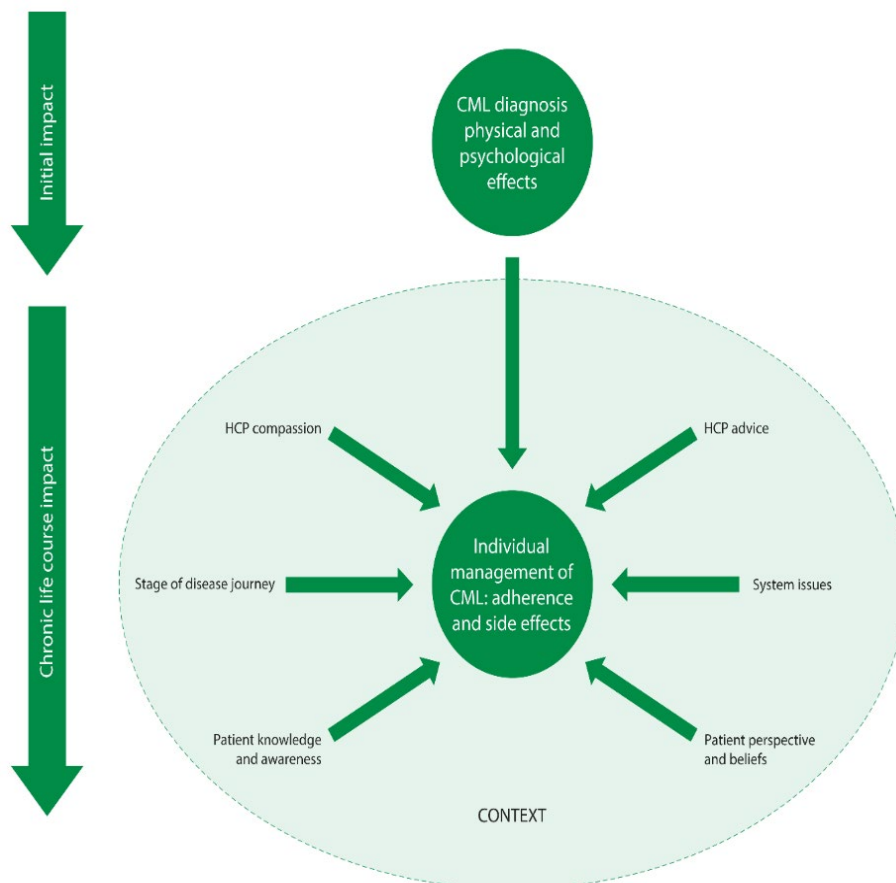
around to make new, logical connections between themes in a way that clearly portrayed the experience of living with CML as described by the papers in the synthesis. Such 'visual mapping' is recommended by Braun and Clarke (2013) as an important way of conceptualizing relationships, and it enabled me to think more clearly about the codes, which I did whilst continually revisiting the coding frame and rereading original texts to check my ideas. Braun and Clarke (2013) describe this process as 'active', where themes are actively created by the analyst rather than merely 'emerging' from the data. Finally, I was able to create three main themes: *'Disease impacts whole life'*, *'Managing the disease is individual'* and *'Valued aspects of care'*, with ten sub-themes. These sub-themes were based on the earlier sub-themes, with colour coding retained to denote which codes from the coding frame applied to which theme.

Finally, I reviewed my themes by returning to each paper and considering if the coded data were fully incorporated (Braun and Clarke, 2013). This proved essential to both refining and understanding the scope of each theme. As I read each paper, I noted concerns, including coded data that: contradicted a theme, required a separate sub-theme, or was not covered by a theme. There was also some overlap between the data in different themes, and some codes that seemed to have become 'lost' in the analytical process. An example was an issue I had grappled with from the beginning. The data under the sub-code *'emotional journey'* fell under the code *'Adapting to/coping with CML'* (within sub-theme *'diagnosis changes daily life'*). All data in this sub-code came from the two papers describing the 'CML journey' (Guilhot et al., 2013; Graffigna et al., 2017), which I was concerned could lose their conceptual interpretations in the synthesis. On reading the coded data, it seemed very similar to the content of the sub-theme *'perspective on life is changed'*, with both describing psychological reactions and thought processes. The *'emotional journey'* data taken from the two papers, describes psychological states and emotions, linked to a 'stage' in the CML process (e.g. 'shock' or 'crisis') at the time of diagnosis. Interestingly, the coded data in *'perspective on life is changed'*, present in nearly all the papers, also related similar psychological states and emotions to a stage in the CML pathway such as at diagnosis, or once treatment had started. This meant the sub-code *'emotional journey'* could be transferred from the code *'adapting to/coping with CML'* and sub-theme *'diagnosis changes daily life'*, to the sub-theme *'perspective on life has changed'*. It was reassuring that the 'stage of CML' interpretation had not been lost and in fact was related to data from other studies.

At the end of this process I checked my coding and themes with senior research colleagues, who reviewed my coding frame against selected papers. After discussion, final themes and sub-themes were agreed upon. These are depicted in figure 8 as a visual map, used to display the analytical themes and demonstrate relationships between them (Braun and Clarke, 2013). The top green

bubble in the figure represents theme one: *'Disease impacts whole life'*, and the initial psychological and physical impact. The central green bubble describes theme two: *'Managing the disease is individual'*, and how patients make their own decisions, particularly regarding the management of adherence and side-effects. Some of the factors influencing self-management are shown around this bubble, including sub-themes from theme three: *'Valued aspects of care'*. This theme explains what patients valued about their HCP, how HCPs delivered advice and information, and suggested improvements in care. The final two themes demonstrate the context of living with CML over a life-time

Figure 8 Thematic synthesis themes



3.3 Findings

I used an illustrative approach when writing the synthesis findings, to depict the data descriptively, rather than analytically. This provided a rich description of the themes and how they are understood, using illustrative quotations in a way that would still make sense, even if the quotes were removed (Braun and Clarke, 2013). As a novice researcher, this seemed appropriate as I had

less confidence in my ability to see the deeper meaning in the data. Also, several papers used this approach, without analytical concepts or models. Each of the three themes separately and its sub-themes, are described using direct quotations or authors comments as supportive evidence. Where a quotation specifies “(...)”, this indicates some text has been removed which isn’t relevant to the issue being discussed. Where a quotation specifies “[text]” a word(s) has been added by myself to help explain the quotation. It is important to point out here that one paper (Wu et al, 2015) included practitioner participants in addition to patients, so some quotes are directly from them rather than their patients. However, as a result of the coding process, I did not identify a theme specifically related to the practitioner role, so their data was coded within the existing themes. The findings are presented as a descriptive account, however, the themes themselves are analytical due to the analytical process (described earlier) used to create them.

3.3.1 Theme 1: Disease impacts whole life

This theme describes the physical, psychological and practical impact of living with CML. It is the first theme presented as it provides the ‘backdrop’ to the CML experience, describing how each area of life is affected.

Sub-theme: Patients experience many symptoms and may change drug regimes

This sub-theme illustrates the varied side-effects to treatment, which were widely reported and included pain, skin problems and fatigue, but most commonly nausea and/or vomiting (Bolarinwa et al., 2018; Lim, Eng and Chan, 2017; Mortensen and Mourek, 2017; Tan et al., 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011). Often patients reported these effects in terms of the impact they had on daily life:

“Besides nausea and vomiting, I had ulcers in my mouth, which made it difficult for me to eat.” (Lim, Eng and Chan, 2017, p.1927)

“Tiredness of colossal, you know—I’ve got a young family and just sort of trying to keep up with the daily routine of that is not easy.” (Wu et al., 2015, p.258)

Side-effects were also described in relation to the detrimental effect they had on adherence to medication and the techniques patients used to manage their symptoms (Bolarinwa et al., 2018; Lim, Eng and Chan, 2017; Tan et al., 2017; Chen et al., 2014; Eliasson et al., 2011):

"I felt nausea. I know the medication is expensive, (it would be) a waste if (I) were to take and vomit back out. I did not take." (Tan et al., 2017, p.1030)

"To cope with the adverse effects, participants either reduced the dose of imatinib or adopted other approaches such as taking imatinib with or soon after a meal to reduce uncomfortable nausea or vomiting." (Chen et al., 2014, p.124)

It is worth noting some reports of patients experiencing only mild side-effects (Bolarinwa et al., 2018; Lim, Eng and Chan, 2017; Chen et al., 2014):

"...only 2 participants have experienced some of these side-effects which they described as mild and quickly manage." (Bolarinwa et al., 2018, p.3)

However, this was only once described as mild by patients, with interpretation of this made by the researchers in the other papers (Lim, Eng and Chan, 2017; Chen et al., 2014) for example:

"Although the ADRs [adverse drugs reactions] were generally mild and tolerable, some participants still complained that their daily activities were significantly affected." (Lim, Eng and Chan, 2017 p.1927)

In this quote, it is notable that symptoms described as 'mild' are also said to significantly affect daily life. It is unclear if this is a message patients also receive from their practitioner, and if so, whether this may discourage them from reporting side-effects, an issue discussed later in sub-theme: "*perspective on life is changed*". Some patients who had their medication switched to a second-generation drug due to their symptoms, reported psychological relief at starting a new treatment and a positive effect on daily living (Lim, Eng and Chan, 2017; Mortensen and Mourek, 2017; Guilhot et al., 2013):

"This medication is better because it does not cause severe nausea and vomiting. Therefore, I am able to do my work undisturbed." (Lim, Eng and Chan, 2017, p.1927)

However, there was a single report of a patient declining to switch to a second generation TKI:

“Doctor recommended the new medication to me, but I did not want to change...I cannot take any food for two hours before and one hour after taking that medication (nilotinib), meaning a total of three-hour fasting. I prefer this medication (imatinib) which I can take whenever I wish to.” (Lim, Eng and Chan, 2017, p.1928)

This demonstrates patients as decision makers, who may decide not to follow recommendations from their doctor, a concept that appears again, in theme 2: *‘managing the disease is individual’*.

Sub-theme: Diagnosis changes daily life

This sub-theme describes the areas of daily life influenced by CML and its treatment, including work, family, sense of self and mood (Bolarinwa et al., 2018; Boons et al., 2018; Graffigna et al., 2017; Lim, Eng and Chan, 2017; Mortensen and Mourek, 2017; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013; Eliasson et al., 2011). In particular, the point of diagnosis was distressing due to repeated tests and the wait for results (Graffigna et al., 2017; Mortensen and Mourek, 2017; Guilhot et al., 2013):

“In general, patients perceived the process of multiple assessments and confirmatory tests and the waiting periods for these necessary analyses as extensive, daunting, and agonizing.” (Guilhot et al., 2013, p.85)

This distress is perhaps compounded by reports of several patients being asymptomatic at diagnosis:

“Many were asymptomatic of their CML at diagnosis.” (Wu et al., 2015, p.257)

“Most patients with newly diagnosed CML were asymptomatic, and CML was unexpectedly diagnosed after a routine physician visit.” (Guilhot et al., 2013, p.85)

However, a minority of cases also had non-specific symptoms (Guilhot et al., 2013):

“...a few patients had nondescript aches and pains that led them to seek medical attention, patients generally had primary symptoms that could not be initially explained by physicians.” (Guilhot et al., 2013, p.85)

One paper describes the more serious issue of misdiagnosis (Bolarinwa et al., 2018):

"I was very ill, I could not stand and I have no blood...my husband took me to several hospitals and herbalist homes with no relief. He spent over a million naira...to get me well but my condition did not get better." (Bolarinwa et al., 2018, p.3)

This perhaps represents a lack of resources or belief in divine healing and alternative medicines in the particular study setting. With asymptomatic patients, the shock of being diagnosed with CML is unavoidable, many finding it life-changing and requiring a reconfiguration of their normal routine (Graffigna et al., 2017; Lim, Eng and Chan, 2017; Wu et al., 2015; Guilhot et al., 2013):

"My life collapsed like a house of cards." (Guilhot et al., 2013, p.85)

"The diagnosis was totally unexpected ... and utterly transformed their lives." (Graffigna et al., 2017, p2745)

The effects of the disease and treatment impacted on daily life in many ways, both psychologically and in more practical terms. This impact was frequently reported across the papers (Boons et al., 2018; Graffigna et al., 2017; Lim, Eng and Chan, 2017; Mortensen and Mourek, 2017; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013; Eliasson et al., 2011), with heightened anxiety and health-related worry more profound at diagnosis (Graffigna et al., 2017; Chen et al., 2014; Guilhot et al., 2013):

"I hyper-scrutinized my body in search of new symptoms or signals that my health was worsening." (Graffigna et al., 2017, p.2749)

Other psychological effects reported were low mood and difficult changes in self-identity, role and future plans (Boons et al., 2018; Graffigna et al., 2017; Mortensen and Mourek, 2017; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013):

"I was depressed all the time. I kept going back to the thought of how much time is left to live?...There was no stability in terms of my psychological condition." (Guilhot et al., 2013, p.88)

Practical concerns were also raised regarding employment and finances, either due to side-effects or frequent hospital appointments (Boons et al., 2018; Graffigna et al., 2017; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013):

“Our company is conducting several big projects overseas, such as the manufacture in Vietnam; I have to decline the project because I have my regular appointments.” (Chen et al., 2014, p.123)

Finally, the effect of the patient’s disease and treatment on their family and friends in terms of an altered family role or new tension in relationships was described (Graffigna et al., 2017; Mortensen and Mourek 2017; Eliasson et al 2011). One paper also observed the importance of emotional and practical support family and friends provided, which had enabled patients to cope with the disease burden (Graffigna et al., 2017):

“My family was badly affected by my disease. They were shocked at first, but as time went by they became such an important support for me.” (Graffigna et al., 2017, p.2747)

Patients in one paper reported patients describing an appreciation of a national patient advocacy group (Boons et al 2018). In response to CML, patients adapted new routines to cope and manage, such as changing work commitments or giving up certain hobbies (Graffigna et al., 2017; Chen et al., 2014; Guilhot et al., 2013; Eliasson et al., 2011):

“Two patients experienced side-effects and still took the imatinib as prescribed despite periods of severe fatigue, which had prompted changes in everyday activities.” (Eliasson et al., 2011, p.629)

It is important to note that there were also some reports that living with CML had little impact on daily life, usually following the start of treatment (Mortensen and Mourek 2017; Chen et al., 2014; Guilhot et al., 2013):

“I hardly think of myself as sick. Because I am treated, I’m well. So it doesn’t take up any space in my everyday life.” (Mortensen and Mourek 2017, p.9)

Sub-theme: Perspective on life is changed

This sub-theme explores the impact of CML in more detail by describing the psychological states patients experience post-diagnosis. Although only two papers formally referred to the ‘patient journey’ (Graffigna et al., 2017; Guilhot et al., 2013), all referred to psychological states in relation to where the patient was in terms of their diagnosis and treatment (Bolarinwa et al., 2018; Boons et al.,

2018; Lim, Eng and Chan, 2017; Mortensen and Mourek 2017; Tan et al., 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011). Here, Graffigna et al (2017) describe the CML journey:

“The patients’ narratives were replete with feelings and emotions, and they gave testimony to the ‘illness journey’ from the initial shock of being diagnosed with the disease to battling against it with strength and courage, and eventually, as time passed, better acceptance of their state of health.” (Graffigna et al., 2017, p.2750)

As previously described, the impact of CML can change familiar daily routines. The first psychological stage relates to this. Described as the ‘shock’, ‘anxious alert’ or ‘crisis’ period (Graffigna et al., 2017; Guilhot et al., 2013) following diagnosis, patients felt pessimistic and sometimes fearful of the future (Graffigna et al., 2017; Guilhot et al., 2013):

“At the beginning I was dead.” (Graffigna et al., 2017, p.2749)

“At that stage I was certain that ‘the worse’ was still to come.” (Graffigna et al., 2017, p.2749)

Almost marking the end of this period are reports from patients of relief that successful treatment was available (Graffigna et al., 2017; Guilhot et al., 2013):

“Patients were very relieved to learn that multiple TKI therapies were available to them.” (Guilhot et al., 2013, p.88)

The process of adaptation follows shock, and conveys a dissipation of previous anxiety and a general acceptance of the disease and treatment (Bolarinwa et al., 2018; Graffigna et al., 2017; Lim, Eng and Chan, 2017; Mortensen and Mourek 2017; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013; Eliasson et al., 2011). Many papers described patients accepting the reality of the disease and seeing it as a chronic illness:

“...now I know what I have, and I’m moving on.” (Guilhot et al., 2013, p.88)

“Most participants regarded CML as a ‘chronic disease’.” (Chen et al., 2014)

This often seemed to be described alongside a growing knowledge and understanding of the disease, blood results indicating a good response, and practical adjustments to daily activities:

"...as time passed, they started to acquire better knowledge of their health condition and of its prognosis." (Graffigna et al., 2017, p. 748)

"Becoming relaxed with taking imatinib as responding well." (Eliasson et al., 2011, p.628)

"It was all about the children before, educating and dressing them... Now I pay attention to myself more. I listen to myself and to when my body says." (Guilhot et al., 2013, p.89)

Adaptation therefore, seemed not to be merely time-related, but an active process by the patient, influenced by their treatment and care. At the point of acceptance, one paper reports patients found talking about the disease was easier, indicating a good time for practitioner intervention:

"It took quite a long time until I was able to talk about it this easily. First, I had to accept it for myself." (Guilhot et al., 2013, p.89)

Two papers (Mortensen and Mourek 2017; Guilhot et al., 2013) also report patients diagnosed more recently found the adaptation process easier and were generally less anxious, perhaps due to the availability of more effective modern treatments and a better prognosis. Those with an older diagnosis, with experience of less effective treatments, may have had much more serious concerns and more problems with disease response, or may have been given a worse prognosis, making adaptation harder.

"The first half year, I had a lot of fear of death. There weren't many treatment options at that time, but the development since has been amazing... I could feel a sense of safety in my body." (Mortensen and Mourek 2017, p.4)

Patients appeared to gain a more positive perspective as a result of their adaptation (Bolarinwa et al., 2018; Graffigna et al., 2017; Mortensen and Mourek 2017; Wu et al., 2015; Guilhot et al., 2013). Some said they were grateful for their treatment and that accepting it had added value to their life:

"My drug is like a lifesaver" (Graffigna et al., 2017, p.2745)

"... my life became more structured ... one gets to value life more. (Guilhot et al., 2013, p.89)

In addition, some patients reported feeling 'lucky' they had this particular disease, comparing themselves to those with more acute cancers (Bolarinwa et al., 2018; Wu et al., 2015; Guilhot et al., 2013):

"But there's a lot of people in the world worse off than me, and I think myself lucky."
(Wu et al., 2015, p.258)

According to Wu et al (2015), such 'downward comparison' may instil reluctance to seek help from practitioners, as although this perspective provides the patient with a positive outlook, it may lead them to believe any disease or treatment concerns are relatively minor. It could also influence their adherence decisions and the reporting of concerns to practitioners, as discussed in theme two (*sub-theme: patients decide on how to manage their disease and side-effects*). In contrast however, one paper reported patients still experienced feelings of fear and sadness, suggesting that the assumption of a wholly positive perspective following acceptance and adaptation would be wrong:

"I think I've adjusted to CML. Although to be honest I have to say that I still sometimes feel sad." (Graffigna et al., 2017, p.2749)

"Sometimes you just want to be free and normal." (Graffigna et al., 2017, p.2746)

As patients move to a 'new normal' stage (Guilhot et al., 2013) following a process of acceptance and adaptation, they may renew future life plans, which prior to diagnosis could have appeared modest, but take on new meaning post-adaptation (Graffigna et al., 2017):

"I am satisfied with the treatment, this makes me hope to have a future, get married and have a baby. Treatment gives me new hope for my life projects." (Graffigna et al., 2017 p.2746)

Some patients expressed a hope that one day they may be able to stop treatment (Boons et al., 2018; Graffigna et al., 2017; Mortensen and Mourek 2017; Wu et al., 2015):

"I was told... this is my lifeline, (but) I wonder if there's ever a time that I can have a break." (Wu et al., 2015, p.260)

However, alongside patient reports of optimism are accounts of uncertainty and fear for the future (Mortensen and Mourek 2017; Tan et al., 2017; Chen et al., 2014; Guilhot et al., 2013). In particular, patients referred to fear of disease progression:

“The problem is we do not know when the condition will be stable because some of the drugs will cause resistance of your genes, so your genes at the end will eventually go mutated. And that’s very worrying for me” (Tan et al., 2017, p.1031)

This is also evident when patients were asked about the future possibility of stopping their drugs (Graffigna et al 2017; Mortensen and Mourek 2017):

“I worry that if I interrupt the therapy the disease might come back. However, the possibility of recovery fills me with joy and hope.” (Graffigna et al., 2017, p.2748)

One paper reported worries over western medicine and long-term health effects of TKI drugs:

“...However, we worry the long-term use of Western medicine will damage liver or kidney.” (Chen et al., 2014, p.124)

Overall, the data in this theme demonstrate a process that patients actively participate in, in order to accept the disease and adapt psychologically. Although many patients travel from shock, to adaptation to a ‘new normal’, emotions may vary at these stages so cannot be assumed. Despite an initial dissipation of anxiety, this may resurface following adaptation in the form of fear of disease progression. Mood may also be low at the time of acceptance as patients reflect on the reality of their changed life.

3.3.2 Theme 2: Managing the disease is individual

This second overarching theme captures, in more detail, the patients’ behaviour in terms of disease management including the management of side-effects, adherence and level of disease awareness. This behaviour appears to be based on decisions made by the individuals themselves on a conscious level and these decisions seem to lie within the context of other influences such as advice from practitioners and the availability of drugs.

Sub-theme: Patients decide on how to manage their disease and side-effects

As described earlier, commonly patients reported gastro intestinal side-effects to TKI drugs, but also other symptoms including tiredness and muscle pain (Bolarinwa et al., 2018; Lim, Eng and Chan, 2017; Mortensen and Mourek 2017; Tan et al., 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011). Patients developed ways of managing such symptoms, including timing the dose around

meals and taking it at bedtime to reduce the effects of nausea (Lim, Eng and Chan, 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al 2011):

“I changed to take the medicine before bed-time or after a meal. If I take it with an empty stomach, I will definitely vomit it out in ten minutes.” (Chen et al., 2014, p.124)

Some took complementary and alternative medicines to either deal with side-effects or for their general health (Bolarinwa et al., 2018; Wu et al., 2015):

“The drops that (the naturopath) gave me to put under my tongue, they sort of seemed to work for me...there’s nothing wrong with having a go.” (Wu et al., 2015, p.258)

Two papers reported patients receiving alternative medicine when first ill pre-diagnosis with no benefit (Bolarinwa et al., 2018, Tan et al., 2017), or as an alternative to TKIs, leading to non-adherence:

“When I fell ill, I was admitted in several hospitals with different diagnoses. I received different treatments and herbal drugs with little or no relief.” (Bolarinwa et al., 2018, p.3)

“They said but I cannot take it together with the medication from the doctor, so I stopped the medication for a month. Then that’s it, my condition was worsening.” (Tan et al., 2017, p.1031)

There was some indication that practitioner advice could be lacking about side effect management (Boons et al., 2018; Wu et al., 2015) and that treatment for side-effects could be inadequate (Tan et al., 2017):

“My experience is that (the haematologist) did not want to talk about side-effects...And motivates this by saying: if we are talking about side-effects it could trigger its occurrence.” (Boons et al., 2018, p.647)

Indeed, whilst there is a suggestion of some patients consulting practitioners about disease related issues such as stopping medication, there seems to be a consistent finding that patients had a tendency not to consult their practitioner, usually in relation to non-adherence but also side-effects (Boons et al., 2018; Lim, Eng and Chan, 2017; Tan et al., 2017; Wu et al., 2015; Eliasson et al., 2011). Therefore, as practitioners may simply be unaware of side-effects and symptoms, they are unable to

provide support. Where reasons for non-consultation are given, these included not wanting to bother the doctor or thinking the matter unimportant:

“I do not want to go to the doctor too frequently. I can judge it by myself.” (Lim, Eng and Chan, 2017, p.1927)

There was a suggestion that improving patient awareness and education could promote reporting to practitioners (Boons et al., 2018; Wu et al., 2015):

*“there are a lot of resources around, but just making [patients] aware was the issue.”
(Wu et al., 2015, p.259)*

Sub-theme: Patients make their own decisions about adhering to their medication

This sub-theme again demonstrates individual thought processes around adherence, with many strategies employed to help patients take their medication as prescribed, including routine and forward planning, family support and the use of alarms and devices (Bolarinwa et al., 2018; Boons et al., 2018; Lim, Eng and Chan, 2017; Mortensen and Mourek 2017; Wu et al., 2015; Guilhot et al., 2013; Eliasson et al., 2011):

“[My medication] is in the kitchen for breakfast or in my purse when I go to work. I never miss a dose and it’s a ritual every morning.” (Guilhot et al., 2013, p.88)

“My husband reminds me to take my drug, at times my phone ring when it gets to the time to take it, I have never missed it.” (Bolarinwa et al., 2018, p.4)

However, there were times when patients intentionally decided not to take their medication. This occurred for varied reasons, although most commonly to avoid side-effects and enable eating and drinking on social occasions, or when ill with other ailments (Bolarinwa et al., 2018; Boons et al., 2018; Lim, Eng and Chan, 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011):

"...I thought there was no way I was going [on holiday] and being tired. So I did actually stop taking the tablets for a week before I went, and I didn't take them for the first half of the week I was there." (Eliasson et al., 2011, p.629)

"I went off my pills for three days, and for the wedding the food was beautiful and the wine was lovely and everything tasted so good [be]cause everything tastes so rotten when you're on Glivec." Wu et al., 2015, p.258)

"If I have a flu or fever, I will reduce the dose by myself." (Lim, Eng and Chan, 2017, p.1927)

Other reasons for intentional non-adherence included travel/holidays, religious observance, fear of harm from TKIs, possible pregnancy and belief in alternative medicine:

"I know it should be taken every 12 hours, but instead I have been taking it at 16-hour and 8-hour intervals during Ramadan. The doctor advised me not to fast; however, as a Muslim, fasting is one of the Five Pillars of Islam." (Lim, Eng and Chan, 2017, p.1927)

Patients then decided whether to compensate for the missed medication (Lim, Eng and Chan, 2017; Wu et al., 2015; Eliasson et al., 2011), with some always doing this as soon as they remembered, usually the same day:

"I sometimes missed a dose, but have never waited until the next day. Most of the time, I forgot to take the medication in the morning, and took it when I remembered in the afternoon or evening." (Lim, Eng and Chan, 2017, p.1927)

However, more of the data describes how most patients did not compensate for missed tablets (Lim, Eng and Chan, 2017; Wu et al., 2015; Eliasson et al., 2011), with further explanations for this, including not wanting to bother the doctor:

"I forgot to take the medicine with me. I'm a little bit worried, but I say no it's too late now and I don't want to tell the doctor, I don't want to upset the doctor." (Wu et al., 2015, p.258)

As well as deciding they could judge whether to change doses themselves:

"I do not want to go to the doctor too frequently. I can judge it by myself, as I know my condition very well. If I have a flu or fever, I will reduce the dose by myself." (Lim, Eng and Chan, 2017, p.1927)

Many patients expressed a belief that missing an 'odd dose', or sometimes more, would not be detrimental to their health and was not a cause of concern (Boons et al., 2018; Mortensen and Mourek 2017; Tan et al., 2017; Wu et al., 2015; Eliasson et al., 2011):

"I get into the car, due to take off and remember about that, and I say, "Ah, only one day"; don't worry about that." (Wu et al., 2015, p.258)

This may have been partly due to a reliance by patients and practitioners on molecular blood monitoring to indicate any problems as a result of non-adherence, or as an indicator of non-adherence, which could be reassuring for patients:

"...I suppose if they noticed that there was something wrong then they would say, you know, make sure you take the full dose." (Eliasson et al., 2011, p.629)

"I don't expect it is noticeable in my blood...as long as the blood results are good, I do understand it is not smart, but, well, you get away with it, so to speak." (Boons et al., 2018, p.646)

Sometimes practitioners' advice reinforced the notion that missing doses may be acceptable:

"I've missed a couple of nights and I've rang like the research nurse and she said, 'Look, don't stress. It's only one night.'" (Wu et al., 2015, p.260)

Furthermore, some patients reported feeling better after missing doses, due to reduced side-effects:

"...I really noticed it when I didn't take it for 2 months...I felt myself again." (Eliasson et al., 2011, p.629)

Finally, data from two papers suggests that adherence behaviour can change over time (Wu et al., 2015; Eliasson et al., 2011). This shows that whilst some patients reported worse practice soon after diagnosis, this improved as they 'got used to' the medication; others become less receptive or lost motivation to adhere over time after receiving a good response to their medication. Therefore,

similar to the data on psychological stages on the disease journey and emotional perspectives, adherence behaviour cannot be predicted based on time since diagnosis:

“Five other patients who also experienced change said it took time to get used to taking the imatinib and that they might have missed more doses in the early days of treatment.” (Eliasson et al., 2011, p.629)

“One pharmacist (HP8) stated, “If these patients have had [CML] for a while they’re less receptive; they don’t want to hear [the advice] again.” (Wu et al., 2015, p.260)

Sub-theme: Influences on adherence

Despite the patient’s own decision process involved in medication adherence, this sub-theme places decision-making into the context of the patient’s life, within influences from the health system, their social situation, deeper motivations and susceptibility to human error. Unintentional non-adherence was commonly described by patients (Bolarinwa et al., 2018; Boons et al., 2018; Graffigna et al., 2017; Lim, Eng and Chan, 2017; Tan et al., 2017; Wu et al., 2015; Eliasson et al., 2011), the most common reason for this was the patient forgetting to take their medication, either due to a change in routine or travelling, but often the patient simply forgot:

“My drug is my life, I try to follow the dosage on the doctor’s prescription, but it might sometimes happen that I forget.” (Graffigna et al., 2017, p. 2746)

Problems accessing medication and costs to patients in certain countries, such as transport costs and disease monitoring, were also described as causing unintentional non-adherence in three papers (Bolarinwa et al., 2018; Graffigna et al., 2017; Tan et al., 2017):

“We want to go to the hospital, there’s no vehicle, vehicle got to pay, that is difficult. Go once can, second time can, third time cannot go already because of insufficient finance.” (Tan et al., 2017, p.1032)

Unintentional adherence was sometimes due to prescription errors:

“...one patient could not get the prescription dispensed at the pharmacy and was therefore not able to take any imatinib for some days.” (Eliasson et al., 2011, p.627)

Communication issues were cited as a barrier to adherence, with some practitioners reporting difficulties communicating in a different language, patient difficulties accessing medical advice or problems between pharmacy and medics (Wu et al., 2015; Eliasson et al., 2011)

“...even adherent patients intentionally skipped doses if there were difficulties accessing timely assistance or were unwilling to seek help.” (Wu et al., 2015, p. 261)

Several papers picked up on beliefs patients attached to their medication, which effected their adherence motivation (Bolarinwa et al., 2018; Boons et al., 2018; Lim, Eng and Chan, 2017; Mortensen and Mourek 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011). Some reported having faith in their doctor and treatment, which improved their adherence:

“...It’s a belief really, that’s keeping me going. I’ve now put all my faith in [the imatinib]. From day one I’ve got faith in [my clinician].” (Eliasson et al., 2011)

There were also accounts from patients that fear of progression motivated adherence:

“too scared not to be on it, so I really, you know, I don’t want to miss it.” (Wu et al., 2015, p.259)

Others described themselves as ‘conformist’ in their following of doctor’s advice, which prompted them to adhere:

“In both cases the patients described themselves as ‘conformists’ who did what the doctor prescribed.” (Eliasson et al., 2011, p.628)

Interestingly, whilst some patients adhered because they did not experience side-effects, others did so despite side-effects:

During the weekend I drink two glasses of wine during dinner. I can’t drink more, because otherwise I will suffer from diarrhoea. But, compared to not being there anymore... well, then I’d rather take the pills.” (Boons et al., 2018, p.646)

Data about practitioner’s advice conveys that the information given to patients encouraged a high level of adherence (Bolarinwa et al., 2018; Wu et al., 2015; Eliasson et al., 2011):

"I often sort of talk about routine, you know, talking about the fact that it is with a main meal and which main meal is the most consistent throughout your day." (Wu et al., 2015, p.258)

Yet the data also suggests some practitioner advice reinforced non-adherent behaviour through directly advising that missing an odd dose is acceptable, or patients misinterpreted advice that their disease response remaining stable meant that missing their medication was safe (Wu et al., 2015; Eliasson et al., 2011):

"...I am tending to miss more now, because at first I thought it was sort of life or death if you miss a tablet, but now the doctors have told me, you know, it's not a big thing if you miss one or two, so I tend to not worry about it as much as I did previously." (Eliasson et al., 2015, p.629)

Adding to this complexity, the data also suggests patients were less likely to inform practitioners when they had missed a dose (Lim, Eng and Chan, 2017; Tan et al., 2017; Wu et al., 2015; Eliasson et al., 2011). Where given, reasons for this were that patients thought it wasn't important or could judge for themselves:

"I was unable to hear for about a week, so I self-adjusted the dose. For example, if I was taking 200mg, I reduced it to 100mg during that week. I did not seek the consultation from doctors because my next clinic visit was 3 months after that." (Lim, Eng and Chan, 2017, p.1927)

Therefore, if the blood level response was unaffected and the patient didn't report their non-adherence, it may remain unknown to the practitioner.

Sub-theme: Patients have varying disease knowledge and need for knowledge

This sub-theme describes how patients' knowledge and understanding differs, as does the desire for information. One paper reflected on variation in the need for knowledge according to psychological stage of the CML journey (Guilhot et al., 2013). It seems reasonable to assume that level of knowledge and understanding could influence patient management of their disease, including side-effects, adherence and reporting to practitioners (Graffigna et al., 2017; Lim, Eng and Chan, 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011). There were some examples of patients showing awareness of what CML is and how it affects the blood cells:

“Patients described CML as a serious disease but no longer perceived it as fatal. They showed a good level of literacy about it and an awareness (or rather a hope) of potentially being able to recover from their condition.” (Graffigna et al., 2017, p. 2749)

However there appeared to be more accounts of patients’ lack of knowledge about the disease and in particular, it’s treatment (Boons et al., 2018; Lim, Eng and Chan, 2017; Tan et al., 2017; Wu et al., 2015; Chen et al., 2014; Eliasson et al., 2011). Some patients felt that they had a certain amount of medication ‘stored’ in their body, others said that the medication takes a while to reach effective levels, or conversely, that it works immediately:

“I reckon there’s enough in my system to miss out one day.” (Wu et al., 2015, p.260)

Some patients seemed unclear on indicators of disease progression or did not fully understand disease monitoring:

“...the nurse insisted that I need to have a regular check, that’s strange, I can’t see why it’s necessary.” (Chen et al., 2014, p.123)

Other anxieties related to misunderstandings were expressed, such as believing that resistance to TKIs could develop similar to antibiotic resistance, or that gene mutation and drug resistance is inevitable, that side-effects are an indicator of disease progression, or that the improvement of symptoms indicates a good response despite a poor molecular response (Tan et al., 2017; Chen et al., 2014):

“Compared to the times I was sick, my weakness has reduced. Stomach has already healed, back to normal. I think this medication gives good effects, but doctor said it does not reflect well on my body.” (Tan et al., 2017, p.1030)

Some patients felt they were given too much information (Boons et al., 2018), and there was data from other papers suggesting some either had a minimal need for information in terms of monitoring their disease or were happy to leave the interpretation of their results to their practitioner (Mortensen and Mourek, 2017; Wu et al., 2015; Guilhot et al., 2013):

“Actually, I only want to know that everything is alright... I don’t really mind what it is called exactly and what specific scores these are.” (Guilhot et al., 2013, p.85)

Whereas some data suggested patients may prefer to manage their own results:

"I get the results personally, read them first, and bring them to my doctor." (Guilhot et al., 2013, p.85)

One paper reported some patient's use the internet to find information, but that this could be unreliable and overwhelming (Boons et al., 2018). As discussed in theme 1 (*sub-theme: perspective on life is changed*), two papers described the 'emotional journey' associated with CML and highlighted how patients' need for knowledge and information varied by the stage in this journey (Graffigna et al., 2017; Guilhot et al., 2013). During the 'crisis' or shock' stage when initially diagnosed with CML, patients had little need for information other than that provided by their practitioner and had only simple understanding of the disease and it's treatment:

"...during the crisis stage, sources on CML were not readily available for patients, who heavily relied on their HCPs for information." (Guilhot et al., 2013, p.90)

However, Guilhot et al (2013) found that patients did not necessarily receive all the required information at this stage:

"Treatment milestones were not discussed in detail, but physicians explained that the patient must achieve a good response or 'get to zero'." (Guilhot et al., 2013, p.87)

During the 'adaptation' phase following this, patients tended to seek more information and were disappointed by how little was offered by their practitioner:

"Patients said that their HCPs provided little to no guidance on how to properly take their therapy and that they implemented their own methods to standardize their drug-taking routines." (Guilhot et al., 2013, p.88)

At the stage following this, where patients have come to terms with their disease and reached a 'new normal', anxieties decreased and the need for information was minimal:

"...because patients had fewer worries about their disease at this stage, information-seeking activities generally declined." (Guilhot et al., 2013, p.89)

The data within this theme indicates that individual patients experience an individual decision-making process in managing their disease and medication, and that this is also affected by various

outside influences, including the care and advice provided by practitioners. Consequently, the last section will consider practitioner activities and the value patients placed on clinical staff. This section also discusses improvements that can be made in CML care, which may enable practitioners to influence how patients manage their disease.

3.3.3 Theme 3: Valued aspects of care

This final theme describes advice provided by practitioners, patients' perspective of positive aspects of their care, and the message patients receive about their diagnosis. Improvements to care suggested by patients and practitioners reflect some of these issues.

Sub-theme: Practitioner advice is information based and sometimes lacking

Practitioner advice was often described in the papers in terms of adherence (Bolarinwa et al., 2018; Wu et al., 2015; Eliasson et al., 2011). Data from practitioners and patients emphasised the provision of education to promote adherence:

"HPs believed patient education was the main strategy to encourage adherence." (Wu et al., 2015, p.259)

More specifically, practitioners provided advice on dealing with side-effects, and sometimes used fear of progression to encourage adherence:

"One nurse (HP1) warned patients that CML could be "a devastating disease that can lead to your death," using fear of disease progression as motivation for adherence." (Wu et al., 2015, p.259)

As discussed earlier, conflicting advice was given about missing medication (Wu et al., 2105; Eliasson et al., 2011):

"Twelve out of 21 patients made comments in relation to receiving feedback that seemed to have reinforced the belief that 'occasional' nonadherence did not matter." (Eliasson et al., 2011, p.628)

Data also revealed areas where healthcare professional support may have been lacking (Boons et al., 2018; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013; Eliasson et al., 2011). Contrary to the above data, there were also reports from patients that little advice was provided about drug taking routines and how to deal with side-effects. Other areas of concern where patients reported a need

for more information included sexuality, hospital visit frequency, setting up social care, and impact on daily life:

“Patients said that their HCPs provided little to no guidance on how to properly take their therapy.” (Guilhot et al., 2013, p.88)

“When I vomited, the information wasn’t there; do I take another dose, don’t I, will I overdose?” (Wu et al., 2015, p.260)

Boons et al (2018) reported patients wanting information that was honest, accurate and reliable, avoided medical terms and was easy to understand:

“Not with all those complicated names and medical language (...) Just use basic words.” (Boons et al., 2018, p.647)

One practitioner suggested difficulties with healthcare budgets, and limited time and support in the community, which prevented greater patient support (Wu et al., 2015):

“a pharmacist...acknowledged that her contact with patients was ‘only a few minutes at a time’.” (Wu et al., 2015, p.259)

Data also suggested a lack of practitioner awareness about the extent of non-adherence with some suggestion this was due to a reliance on blood monitoring and/or simply not asking the patient, as discussed earlier (Wu et al., 2015; Eliasson et al., 2011):

“I wouldn’t be aware of [nonadherence] because I’ve never asked them specifically; I just ask them a very general open-ended question.” (Wu et al., 2015, p.260)

“data thus suggest that HCPs tend to focus on giving patients positive feedback regarding clinical response, while patients seem to rely on the clinician to let them know if their response is being negatively affected by their nonadherence (of which the clinician was not aware).” (Eliasson et al., 2011, p.630)

Data also pointed to a lack of support from community health care services, patients commenting that their GP and local chemist had little CML knowledge (Wu et al., 2015; Eliasson et al., 2011):

“Sometimes when you’re talking to the GPs or even chemists, like you know more about CML than they do.” (Wu et al., 2015, p. 260)

Sub-theme: Patients value a caring attitude, reassurance and accessibility in their practitioner

Several papers described what patients appreciated in their relationship with healthcare professionals. This often came in the form of accessibility, reassurance and a caring attitude. Patients emphasised psychological support offered by practitioners, rather than the provision of education and advice (Bolarinwa et al., 2018; Boons et al., 2018; Lim, Eng and Chan, 2017; Mortensen and Mourek, 2017; Guilhot et al 2013;; Eliasson et al., 2011):

“I was shocked when I was first diagnosed with this disease, but my doctor gave me encouragement. He assured me that this medication will help me, so I felt more relaxed.” (Lim, Eng and Chan, 2017, p.1927)

“...my Doctor make sure I get it even during Doctor’s strike, he also calls me to find out how I am doing.” (Bolarinwa et al., 2018, p.3)

Some patients also discussed trust or faith in their practitioner and appreciated continuity from the same individual (Boons et al., 2018; Lim, Eng and Chan, 2017; Guilhot et al., 2013; Eliasson et al., 2011):

“I feel that I am in very good hands. I trust my doctor fully.” (Guilhot et al., 2013, p.85)

Interestingly, there were several instances in one paper of patients reporting that their practitioner presented CML as a ‘low key’ disease, suggesting treatment is simple and prognosis good, advising patients they should not worry (Guilhot et al., 2013):

“The doctor told me I was lucky to have chronic leukemia, because if it was acute, I wouldn’t survive.” (Guilhot et al., 2013, p.88)

Whilst this message is important in alleviating anxiety, it could also play down the disease and its treatment, which could create the notion among patients that they should self-manage their CML. This is similar to the idea of “downward comparison” noted by Wu et al (2015) and may contribute to a lack of patient reporting to practitioners and seeking information. It could also help explain why professionals sometimes failed to give advice or show awareness of certain issues. This communication between patient and practitioner is eluded to in the following sub-theme through

descriptions of potential improvements to care, in addition to more practical suggestions relating to the patient-professional consultation and resources.

Sub-theme: Improvements in care should be interpersonal and resource based

Much of the data regarding possible improvements in care comes from researcher's interpretations of their study findings, similar to 'second order interpretations' (Schutz 1962). Several papers suggested improving patient/practitioner consultations (Bolarinwa et al., 2018; Lim, Eng and Chan, 2017; Wu et al., 2015; Chen et al., 2014; Guilhot et al., 2013; Eliasson et al., 2011). Data recommended that information and advice from practitioners could be improved across a range of areas, including treatment options, managing side-effects, dealing with missed doses, monitoring response and establishing a drug taking routine, with some emphasising the need for this information to be individualised:

"Dialogue about the importance of adherence, management of any adverse events, and potential next steps in therapy can assist patients in establishing a new normality by providing support for adjustments and lifestyle adaptations." (Guilhot et al., 2013, p.91)

"...besides the safety profile and efficacy of TKIs, the physicians should also take the patients' perspectives into consideration when evaluating the best treatment choice for each individual." (Lim, Eng and Chan, 2017, p.1928)

Providing extra telephone support and using services outside of the doctor/nurse appointments such as pharmacy was also suggested:

"Someone like an outreach pharmacist or a nurse could just give them a courtesy phone call and just say okay, so how many tablets do you think you've missed?" (Wu et al., 2015, p.258)

The papers advised that open, non-judgemental dialogue considering the patient's personal 'narrative' should be established by practitioners. This can encourage patients to communicate their anxieties, be honest about adherence; as well as supporting the changes to day to day life that are needed to incorporate their treatment:

"...open communication will be beneficial to the patient in the management of CML throughout his or her journey." (Guilhot et al., 2013, p.91)

This emphasis on individualised care and a non-judgmental approach reflects previous data from patients regarding the value they put on the caring attitude of practitioners. In terms of healthcare resources, two papers presented patient and practitioner data suggesting a need for more ‘people’ resources, including clinic staff, CML patients trained to ‘counsel’ others and specialist nurses to monitor adherence (Bolarinwa et al., 2018; Wu et al., 2015):

“I believe people living with the disease who are also on treatment could be trained as counsellor.” (Bolarinwa et al., 2018, p.5)

Regarding facilities and cost, longer term prescriptions were suggested by patients in one paper (Chen et al 2014), reflecting one of the influences on adherence discussed earlier:

“...a two-week schedule just passes too quickly, we should be allowed to have a long-term drug supply and only come to visit the doctor when we don’t feel right.” (Chen et al., 2014, p.124)

One paper in particular, from a resource-scarce country, presented several patient suggestions, including improving monitoring facilities and lowering the cost to patients, increasing the number of hospitals which can provide CML treatment, and clinic facilities such as toilets and seating (Bolarinwa et al., 2018):

“Some respondents believe increasing the number and spread of hospitals giving the drugs will improve their care and reduce the waiting time at the hospital.” (Bolarinwa et al., 2018, p.4)

Two authors discussed how adherence measures could be improved, suggesting the use of multiple measures and the need to ascertain an objective, ‘true’ level of adherence (Wu et al., 2015; Chen et al., 2014):

“Measuring the true adherence rate among patients could establish a set of feasible targets for intervention.” (Wu et al., 2015, p.262)

This sub-theme reflects on how care can be improved, highlighting awareness in the literature of a need to improve communication and the relationship between practitioners and patients, in addition to concerns regarding resource availability.

3.4 Summary

3.4.1 Strengths and limitations

Publication of this work in a peer-reviewed journal resulted in this being the first documented qualitative synthesis to report on studies of living with CML and managing TKI medication (Hewison et al 2020: see appendix 4). For this reason, it was not possible to compare my findings and conclusions with other work. The included studies originating from different countries, some of which described systems of free access to TKIs, but others that did not clarify this. However, as inclusion criteria for all the studies stated receipt of TKIs, it is assumed that patients could access their medication. Also, as findings were relatively consistent amongst studies, it is expected that my analysis is largely transferable to other regions with similar health systems. Major strengths include a robust search strategy, study eligibility, codes and themes checked by two researchers, and the use of NVIVO software to facilitate data management and retrieval. The search for articles was last updated July 2020 and now includes 371 patients, which is an increase from the time of the published synthesis.

Each included study had its own limitations. Overall, several lacked a comprehensive report of their methodology, notably sampling strategies (e.g. inclusion criteria and reporting on excluded participants), and explanation of theoretical models applied to data analysis. For example, as discussed earlier, Wu et al (2015) used interpretative phenomenological analysis (IPA), but did not describe how its features were implemented in the analysis, such as the impact of the researchers' own conceptions on the findings. However, the included studies showed strengths in the reporting of their findings. Although this varied from descriptive to more conceptual accounts, there was consistency between the data and results, quotations were used appropriately, and findings were generally presented clearly.

3.4.2 Summary of synthesis findings and application to practice

Overall, data from the ten qualitative papers in this synthesis provides an overview of the physical and psychological impact of CML and its effect on daily life and on life perspective. It describes the complex decision-making process involved in managing CML and how this may be influenced by individual and broader contextual factors. It suggests that whilst practitioners may concentrate on the provision of information and advice, patients emphasise the value of emotional aspects of the practitioner/patient relationship. Suggested improvements to care reflect this, in that they are both information/resource based, as well as concerned with the 'softer', patient facing aspects of care. Bringing the ten papers together in a synthesis provides a more complete understanding of the

complexity of the CML experience, as each paper had a different focus. The synthesis also suggests some explanatory factors about patient behaviour and care, which may support practitioners' delivery of care. In conclusion, I have summarised and directed my synthesis findings into areas of relevance to practice, to reflect one of the main objectives of the overall thesis.

Data from one paper (Guilhot et al., 2013) suggests practitioners may infer that CML is a 'low key' disease, which should not cause patients worry; and others discuss the 'downward comparison', when patients compare themselves to 'people worse off' (Bolarinwa et al., 2018; Wu et al., 2015). However, much of the data indicates that CML has a far-reaching effect over many aspects of daily life, both physical and psychological, suggesting that this disease is not a simple experience to the individual. Gastro-intestinal effects were common, diagnosis distressing, and changes to work and family life required. The papers also suggest that patients are less likely to report side-effects and non-adherence to their practitioner, and can be living with worries about their future and trouble with their mood at diagnosis, and as they adapt to the disease. Advice framed within the understanding that patients may find CML complex and difficult to deal with, can be more helpful in encouraging patients to report side-effects, non-adherence and psychological difficulties.

All the included studies suggest patients experience certain psychological stages in the 'CML journey' from diagnosis onwards. An initial shock, followed by a process of adaptation and then a 'new normal', seemed to resonate with all the papers. However, the data indicated that moving through the stages was not merely a matter of time, but an active process for the patient. Learning about the disease and its treatment, gaining a good response to TKIs, and making practical adjustments to daily life all occurred during adaptation process. As the patient is actively making changes at this time, they may be receptive to practitioner interventions, such as establishing a medication routine, which would provide support to patients and positively influence their day to day life. Furthermore, although most patients reported shock and anxiety at diagnosis, emotional states during adaptation and at the 'new normal' were ambivalent, with both positive and negative emotions described at this time, such as sadness and hope, indicating that time since diagnosis does not always predict emotional state.

Data from the included studies demonstrates the complexity of medication management, with patients making decisions about medication timing to avoid side-effects and determining how to compensate for missed doses. This is set within the context of the patient's life, where both individual and health system factors can influence medication management, including practitioner advice, prescription issues and medication beliefs and motivations. An understanding of how patients make, or would make, decisions in certain scenarios, and what influences this process is therefore valuable in supporting them to optimally manage their disease and treatment. Whilst data

suggest varying levels of information and advice were provided by practitioners, more of the data from patients suggested that a caring demeanour is what they really valued, from a trusted, easily accessible practitioner, who can provide reassurance. These elements may seem obvious requirements, but should not be underestimated, and may equal the impact gained from education and information.

Overall, the synthesis offers a rich description of patient experiences of living with, and being treated for CML, contributing to the thesis aims. Furthermore, it provides evidence to inform practice, another thesis aim, including raising awareness of the complexity and unpredictability of CML and its impact on patients, the timing of advice and encouragement of good decision making. However, whilst the findings offer some advice to practitioners, they were mainly generated from patients' perspectives. Although it is valuable in understanding patient experiences, an insight into practitioner perspectives of providing care would also be beneficial and would ensure evidence is realistic and appropriate within the clinical context. Furthermore, many of the qualitative articles focussed on the experience of taking treatment for CML, and whilst the synthesis suggested that adherence is not an isolated issue, this narrower focus meant contextual factors, such as social support and practitioner care, were not fully investigated. Therefore, exploring the broader patient experience, rather than concentrating solely on a single issue of adherence/treatment, may offer more understanding both of adherence and the experience as a whole. It is the absence of evidence around this broader experience that led me to conduct in-depth interviews with patients and practitioners. The following chapters relate to this part of my thesis, initially describing the qualitative methods used, then focussing on the patient and practitioner interview findings.

Chapter 4 Methodology

This chapter describes the research methods and techniques used to address the aims of this thesis, which are as follows:

- Explore patient experiences of living with CML and managing treatment for CML
- Examine how practitioners manage CML patient care
- Provide evidence that is relevant to clinical practice which could be used to improve the care and support of CML patients

I discuss the relationship of the aims to current theoretical understanding, and how this led to my chosen approach. The research setting and sampling techniques are then described. Qualitative interviews and their potential value, relative to the research question are considered. This is followed by a discussion of the process of thematic analysis. Finally, I consider the generalisability, reliability and validity of the research as the basis for offering a reflexive critique of my approach.

4.1 Ontology and Epistemology

Examining the research aims in terms of their philosophical underpinnings helps to explain why I chose a qualitative approach. Applying debates concerning ontology (beliefs about knowledge and being) and epistemology (that which we know about the social world), helps to understand the philosophy behind this thesis (see Snape and Spencer, 2003). While not a philosopher, I believe it important to locate my thesis within these more theoretical debates, to justify my methodological approach, although as will be seen, my engagement is pragmatic and consistent with the aims of the thesis.

My overarching aim was to conduct a broad investigation of the experience of living with, and managing treatment for CML, and produce findings that are thematically transferable to the CML population and relevant to practitioners. Understanding the experience of living with and managing CML through the individual's perspective, as they generate meaning, suggests the need for a contextual approach (Barbour, 2014; Flick, 2014) and an interpretivist stance, similar to the thematic synthesis question. This philosophy does not believe in a measurable reality that is external to individuals (Snape and Spencer, 2003), as is characteristic of the positivist approach where ideas of knowledge and truth are considered independent from the individual and are objectively measurable (Flick 2014) (also described in chapter 3: qualitative synthesis). Such positivist theory does not permit individual perceptions of their experience, as it presumes this is already known by the researcher. It was, therefore, inappropriate for this thesis which aims to investigate the, as yet unknown, experience of patients living with CML and the practitioners providing care.

The thesis is also inductive in its approach to generating understanding rather than deductive, when a pre-existing theory or hypothesis is tested. However, my intention that findings are transferable to other CML patients and relevant to clinical practice, suggests that there in fact is a shared reality outside of individuals' human minds which can be applied to all (Snape and Spencer, 2003). A philosophy amenable with the interpretivist/idealist stance, as well as the need to ensure some transferability, is Hammersley's (1992) 'subtle realism', which was discussed earlier in the thematic synthesis chapter (chapter 3), and accepts that there is a shared reality outside of us but one can only know this reality through the minds and perspectives of individuals, which are socially negotiated in relation to others. Such investigation of individual perspectives is well suited to qualitative research. Theoretical traditions in qualitative research are influenced by epistemology and ontology stances and in turn, influence the research techniques employed. These traditions are considered in the next section, alongside the chosen approach for this thesis; thematic analysis.

4.1.1 Qualitative research traditions and thematic analysis

In selecting an approach, different qualitative traditions and inductive methods were considered, including phenomenology, ethnography, ethnomethodology, conversation and discourse analysis, symbolic interactionism and grounded theory (and thematic analysis). To ensure my approach was appropriate, I considered the research question, study aims and underpinning assumptions, and my own skills and resources as a researcher (Padgett, 2012; Teherani et al., 2015). Ethnography, ethnomethodology, conversation and discourse analysis, and symbolic interactionism share an interest in exploring everyday interaction and routines, whilst each has an individual focus and technique. For example, ethnography aims to investigate a topic from different perspectives, whilst the researcher is immersed in the subject's environment and typically, but not exclusively, uses participant observation as the main data collection technique (Padgett, 2012; Teherani et al., 2015). Whilst these approaches had some relevance to my thesis aim, for example, observation of hospital CML outpatient encounters, or understanding the phenomenon of CML diagnosis on the individual, I felt they would not fully address the thesis aims. This was not only to explore the CML experience and individual perspective, but to come to an understanding or theory on this experience or perspective which was relevant to clinical practice. In order to achieve this grounded theory and thematic analysis offered a more suitable approach.

Grounded theory endeavours to generate theory from within data (Glaser and Strauss, 1967), and thematic analysis looks to explore and analyse patterns or themes in the data (Braun and Clarke, 2006). However, grounded theory involves an iterative relationship between analysis and sampling, in that theory is developed as data collection progresses, with subsequent sampling based on

theories generated. It also has specific techniques for coding (Pope, C., Ziebland, S. and Mays, N, 2006; Flick, 2014). As a novice researcher, I felt a little overwhelmed by the plethora of qualitative traditions and approaches, and found little practical guidance as to how to carry out research based on their position. Whilst grounded theory offered more in terms of guidance, I was somewhat discouraged by the complexity of this technique, and learnt that studies purporting to follow grounded theory practice, often in reality did not adhere to all its features (Braun and Clarke, 2006). I therefore adopted a pragmatic response, albeit one that recognised the important of transparency and rigour when making methodological decisions. This informs the purpose of this chapter.

Thematic analysis offered an approach to guide the research and is well used by qualitative researchers (Braun and Clarke, 2006, 2013; Pope, C., Ziebland, S. and Mays, N., 2006). It offers a simpler form of analysis, and rather than being an alternative to other traditions, it is both independent of them, yet can incorporate different traditions in its method. However, as epistemological ideas must be specified by the researcher (see previous paragraph) (Flick 2014; Pope, C., Ziebland, S. and Mays, N ., 2006), it is also a flexible method, that is applicable to my thesis aims. The authors consider it ideal for novice researchers, as it describes an analytical process many other traditions begin with (Braun and Clarke, 2006). Simply, it is described as:

“...a form of analysis which has the theme as its unit of analysis, and which looks across data from many different sources to identify themes” (Braun and Clarke, 2013).

It can also go beyond this to identify explanatory relationships between themes, which this thesis aims to achieve, in order to have relevance to practitioners. Its process was briefly discussed in the thematic synthesis chapter as this technique incorporates thematic analysis, however it will also be described in detail later in this chapter. I now give more information about my methods and decision-making processes, as a basis for establishing rigour. My research question reflects an interpretivist stance suggesting that the theory developed is unique and therefore cannot be judged by quality criteria from other paradigms or indeed at all (Mays and Pope, 2006; Popay, Rogers and Williams, 1998). However, in line with the more pragmatic aim reflecting a subtle realism approach, it is also important to provide a clear and transparent account to justify methodological decisions, and allow reflexivity and reflection on myself as researcher and those researched (Hammersley, 1987).

4.2 Setting: YHHN and HMRN

The study is set within the infrastructure of the Yorkshire and Humberside Haematology Network (YHHN: www.yhhn.org), which forms the core of the Haematology Malignancy Research Network (HMRN: www.hmrn.org), a population-based study registering all patients newly diagnosed with a haematological malignancy in Yorkshire and Humberside, including those with CML. YHHN was established in 2004 to generate ‘real world’, evidence-based information about patients with haematological malignancies. It is a unique collaboration between NHS clinical staff and researchers at the University of York. The YHHN area covers a population of around four million, with care provided by 14 hospitals (five multidisciplinary teams) and clinical practice that adheres to national guidelines. As a matter of policy, all diagnoses (> 2200 annually) are made and coded by specialists at a single integrated haematopathology laboratory – the Haematological Malignancy Diagnostic Service (HMDS: www.hmds.info), which ensures complete patient ascertainment.

4.2.1 The YHHN CML patient and practitioner sample

The total number of YHHN patients with CML in 2016 (when interviews commenced) was 443. Of these, 189 (43%) were female and 254 (57%) male. The median age at diagnosis was 58.4 years, with 234 (53%) diagnosed before the age of 60 and 209 (47%) aged 60 years and above. The YHHN area includes two large hospitals with cancer centres, which specialise in cancer diagnosis and treatment, the remainder being “local hospitals” without specialist centres, although patients may travel to their nearest cancer centre for complex or acute treatment. Of the total, 145 (33%) people with CML were diagnosed at a cancer centre and 192 (66%) at a local hospital (the remaining 1% at a private hospital, by GP or other).

Less is known about practitioners working within YHHN hospitals, although good links exist with the clinical staff via YHHN administrative and network meetings, joint research projects and my own links as a study nurse undertaking data collection for YHHN. It is these connections that were used to initiate practitioner sampling.

4.3 Access to the setting/ethics

Ethics approval for my study was obtained from the University of York Health Sciences Research Governance Committee and Leeds West NHS Research Ethics Committee (REC). The NHS REC application was initially submitted to the Health Sciences committee, whose role is to review the ethical aspects of research proposed by its staff and students, with the aim of ensuring “research has met stringent standards of ethical governance”. The committee met and discussed my application on 07/12/2015 and provided feedback, which was discussed with my supervisors, before necessary

changes were made. For example, I was advised by the committee, and acted on their guidance, to state explicitly that patients would not be contacted until they were at least two months post diagnosis. The application and study documents, were then submitted to the Leeds West NHS REC. My primary supervisor and I attended a REC meeting on 13/01/2016, at which concerns were raised that were also acted upon. These included various changes to the paperwork that would be sent to patients and practitioners, for example changing the word “patient” to “participant”, and promoting the study on the YHHN website. These changes were made and favourable opinion was granted on 31/03/2016 (REC 16/YH/0016) (appendix 5 REC approval). The REC approval shows that the original title for my thesis was “sociomedical factors and survival in CML”, the premise being that adherence was associated with socioeconomic differences found in relative survival of YHHN CML patients (Smith et al 2014). A mixed methods approach was initially proposed for the thesis, including qualitative interviews with patients and practitioners, which fed into a patient questionnaire survey. However, after reviewing the literature, it became clear that adherence had many interrelated, overlapping factors, meaning the CML experience as a whole warranted investigation and therefore my title and aims were adjusted to reflect this and a purely qualitative study planned.

4.4 Patient sampling

4.4.1 The patient sampling frame

YHHN has ethical approval (REC 04/01205/69) and Section 251 support under the NHS Act (2006) (PIAG 1-05 (h)/2007). In addition, with permission from their clinical team, we approach patients, provide them with information about YHHN, and invite them to take part in, or opt out of, the study. Patients are also asked whether they will agree to be contacted again for further research. For the patient interviews, only those who had consented to further contact were included in the sampling frame. This reflected 205 (46%) of the total 443 YHHN CML patients, and formed the sampling frame. The characteristics of the total YHHN CML sample were used to ensure representational generalisation, a concept which is considered later in this chapter, when discussing the sampling strategy and transferability.

Patients were interviewed before practitioners, as the initial thesis aim was to understand experiences of living with CML, which was more likely to be captured if heard from the patient’s perspective. Using this approach ensured findings from the practitioner interviews did not define the themes for the patient interviews, thus allowing the patients to identify issues important to them themselves, reflecting the nature of qualitative enquiry (Barbour, 2014). Collecting interview data

from patients and my preliminary analysis also informed the topics for the practitioner interviews and ensured these reflected patient experience, to which practitioners had to respond.

4.4.2 Sample size and frequency of patient interviews

Qualitative research often refers to data 'saturation' when determining an adequate sample size (Hennink, Kaiser and Marconi, 2017; Morse, 2015; Bowen, 2008). However, authors argue that researchers frequently report reaching 'data saturation' without describing the steps taken to make this decision, and suggest a more robust approach is required (Hennink, Kaiser and Marconi, 2017; Morse, 2015; Bowen, 2008). Originating from the specific methodology of grounded theory (Glaser and Strauss, 1967), saturation refers to a distinct methodological approach where repeated data collection and analysis throughout the research process guides the theoretical sampling of participants of interest to the theories being generated (Hennink, Kaiser and Marconi, 2017).

'Saturation' is reached when this process has provided convincing and complete data categories and no new data is required (Bowen, 2008). Use of the term 'saturation' therefore seems inappropriate in studies which do not adopt the grounded theory approach such as in this thesis (Hennink, Kaiser and Marconi, 2017; Malterud, Siersma and Guassora, 2016). However, the general principles of data saturation, the point at which no new data can be gathered and no new codes can be added, (Guest et al., 2006) were incorporated into the data collection and analysis process.

For this thesis, the NHS REC required an estimate of sample size prior to approval and therefore prior to any data collection. A decision was made to interview approximately 15-20 patients and 15-20 practitioners, following discussion with experienced researchers regarding the likely number needed to gather adequate data to confirm a comprehensive range of theoretical categories. This sample size was also influenced by more practical consideration of the time available for interviewing, and the processing and analysis of data by one researcher (Britten, 2006). Finally, the figure mirrors work by Hennink, Kaiser and Marconi, (2017) who examined sample size in qualitative research and found 'meaning saturation' was generally met at around 16-24 interviews. The authors distinguished 'code saturation' from 'meaning saturation', with 'code saturation' occurring when 'no additional issues' were found, the coding list becoming constant and data understood at a descriptive level; and 'meaning saturation' occurring when 'we fully understand issues' and no new elements could be identified. In this context, Hennink, Kaiser and Marconi (2017) found 'code saturation' was reached after 9 interviews and 'meaning saturation' at different points for different codes, being completely achieved after 16-24 interviews.

In order to plan how many participants to contact at any one time, reference was made to an ongoing YHHN interview study that had had a response rate of around 80%, as well as my workload

as a study nurse and my part time role as PhD student. As a result, potential participants were contacted in 'waves' of 2-5 participants with the expectation that 80% would be willing to be interviewed each time. My sampling strategy was considered next, and is now described separately for patients and then practitioners.

4.4.3 Inclusion and exclusion criteria: patients

For the patient interviews, only those who had consented to being contacted again, as part of YHHN, were included in the sampling frame. This naturally excluded those who had not consented, or had not been invited, for example people with dementia or who were too unwell. As the sampling frame is taken from the wider YHHN sample, this study adopts the same eligibility criteria; that patients are diagnosed after September 2004 and live within the YHHN area at diagnosis. Both males and females, aged 18 years and over were included in the sampling frame in order to represent the total YHHN CML sample (discussed later). The decision was made by myself and senior research colleagues to include only those aged 18 and over due to the rarity of CML in those aged under 18. Only those in chronic phase CML were considered eligible, as accelerated and blast phases are less common and treated differently (often like acute leukaemia, with intensive intravenous chemotherapy, as an inpatient), resulting in alternate experiences. Finally, as advised by the Health Sciences Research Governance Committee, only patients who were at least two months post diagnosis were invited to participate. This was to avoid causing undue stress due to premature contact, before diagnosis and treatment had been fully confirmed. Inclusion and exclusion criteria are summarised below:

Inclusion criteria:

- Agreed to contact about future YHHN research projects
- Diagnosed with CML in chronic phase, post-September 2004
- Living in YHHN study area
- Male or female, aged ≥ 18 years
- At least two months post CML diagnosis

Exclusion criteria:

- Had not agreed to contact for future research or unable to provide informed consent
- Diagnosed pre-September 2004
- Living outside YHHN study area
- Aged < 18 years
- Less than two months since CML diagnosis

A later sampling technique, described in the following section, involved Clinical Nurse Specialists (CNSs) recruiting patients of interest which resulted in some people being approached who were diagnosed before 2004 and/or outside of the YHHN area. This was discussed with my supervisors and senior colleagues who felt that the diversity of experience these patients added to the research data was of great value in understanding the CML experience. They advised to continue with the interviews as the main concern was that of informed consent, and this had been assured by the CNSs discussing the study with the patients in addition to my own study information leaflet and consent process.

4.4.4 Patient sampling strategy

Rather than sampling on selected characteristics to match the general population as is done in quantitative research to test a hypothesis (Braun and Clarke, 2013), qualitative research sampling aims to select participants with certain characteristics who can produce data that is broad enough to describe the thematic diversity of experience. Various well regarded sampling methods were therefore considered, with purposive sampling selected as the most appropriate. Purposive sampling aims to intentionally select participants who have certain characteristics which will provide information relevant to the aim of the research (Braun and Clarke, 2013; Sandelowski, 1995). It differs from more established, less strategic methods, such as 'convenience sampling' where participants are selected on the basis of ease of access to the researcher, or 'chance sampling' where participants are selected at an opportune moment. Such methods were not used in this thesis due to the risk of losing valuable data as the selected sample may not have displayed the broad characteristics of interest to the research aims (Barbour, 2014).

I discussed the sampling strategy with my supervisors and senior colleagues and we concluded it was important to select by age at diagnosis and gender, in order to provide what Lewis and Ritchie (2003) describe as representational generalisation; the ability of the sample to represent the larger population of patients from which the sample was taken, which in this thesis is the total YHHN CML population (n=443). The generalisability of qualitative research will be discussed later, however it is important to distinguish here that representational generalisation aims to provide context so readers can determine if findings are relevant to their setting, as opposed to statistical generalisation which aims to draw conclusions from the findings which can be applied to all other CML patients (Robson, 1993). As a result of these discussions, age and gender were added to the sampling strategy as primary criteria, along with care setting (hospital with cancer centre or local hospital), which was also considered to contribute to representational generalisation. Interviewees

were therefore selected, based on age at diagnosis, gender and care setting, proportional to the corresponding categories across all YHHN CML patients.

Finally, as the interviews progressed, I noted that data did not seem to include the breadth of expected experiences, such as difficulty with adherence or poor response to treatment; in fact, interviewees appeared to have had a relatively 'straightforward' experience. To uncover individuals with more challenging pathways, haematology Clinical Nurse Specialists (CNSs) in the YHHN area were asked to suggest such patients who may be appropriate. Barbour (2014) warns that using such 'gatekeepers' may risk them applying their own ideas onto the sampling, however their access to potentially key patients was perceived to outweigh this, as these harder to reach patients would add further to the diversity of my data (Braun and Clarke, 2013). Consequently, for the final wave, YHHN CNSs were contacted by email and asked to identify patients who "may not have had a straightforward experience of diagnosis/treatment". This final stage led to the inclusion of nine patients solely on this basis, without reference to any other primary or secondary criteria. This method of strategic sampling is similar to theoretical sampling (Barbour, 2014; Braun and Clarke, 2013; Ritchie et al., 2003^a). Unique to theoretical sampling, originally described by Glaser and Strauss (1967) and later by others (Barber, 2014; Bryman, 2008; Ritchie et al., 2003^a), is its revisiting of the field of potential participants by sampling participants in stages, in order to confirm or refute emerging theoretical categories (Bryman, 2008). Although not strictly following this process, it was triggered by the need to iteratively sample those with certain characteristics (i.e. difficult treatment experiences), in order to enrich potential theory development. Following seventeen patient interviews, my supervisors and I considered that data saturation had been reached in that no new codes added or themes developed. In addition, I was confident I had met code and meaning saturation as described earlier (Hennink, Kaiser and Marconi, 2017).

Patients were invited to take part by postal pack, each containing an invitation letter, information leaflet and prepaid return envelope, to which it was possible to respond by post, email or telephone (appendix 6 and 7). Only one contact was made, and if there was no response I did not follow this up. The final sampling grid is presented in table 4, showing interviewed participants as their corresponding study codes (bold) and non-responders (grey). Interviews were carried out 18/07/16 to 10/03/17 and thankyou letters sent post interview, with contact details for YHHN and myself.

Table 4: Patient sampling grid

	Male and age at diagnosis <60	Male and age at diagnosis ≥60	Female and age at diagnosis <60	Female and age at diagnosis ≥60
Hospital with cancer centre	PA23 PA27 PA24	PA02 PA11 PA18	PA01 PA06 PA25	PA12 PA22 PA26
'Local' hospital	PA07 PA03 PA05 PA15 PA16 PA32	PA08 PA13 PA17 PA19 PA28	PA09 PA14 PA21 PA20 PA02 PA30 PA31	PA04 PA10

4.4.5 Practitioner sampling

The purpose of interviewing practitioners was to progress and enrich our understanding of the CML experience beyond the patient accounts by understanding this experience from the viewpoints of those providing care within NHS hospital systems. For example, a patient's account of how they understand their prognosis may differ from the account from a practitioner about the advice they give to patients about their prognosis. Using the practitioner interview data in this way is referred to as triangulation and is discussed later in the section on reliability and validity. However, it is important to highlight here that the aim of this qualitative study is not to arrive at an overall 'truth' about the CML experience, but rather to incorporate different viewpoints on the same topic in order to deepen our understanding (Barbour, 2014; Braun and Clarke, 2013). This is also useful, as it connects patient experience to the 'realities' of practice and therefore, ensures any recommendations are able to balance feasibility with desirability.

4.4.6 Practitioner sampling frame

Staff working at hospitals within the YHHN area formed the total sample of practitioners. This includes haematology consultants, junior doctors and clinical nurse specialists, and other staff who may have contact with CML patients such as haematology ward nurses and foundation year doctors. However these latter groups were excluded from sampling as the majority of CML patients are not

seen as inpatients and therefore these staff may have insufficient experience to provide rich data about the care of CML patients. A decision was made that it would not be necessary to match practitioners with patients they cared for, who had also been interviewed, as the aim was not to explore individual differences, but investigate the overall experience of living with, and caring for those with CML.

The target was to recruit 15-20 practitioners for interview which was informed - as with the patient interviews - by previous qualitative YHHN research, with respect to the development of theoretical categories and researcher time. I intended to conduct approximately one per week, via snowball sampling (see below), rather than dispatching multiple invitation letters to practitioners, hoping this would make planning interview frequency simpler. In practice, interviews occurred less frequently than this, due to pressures on NHS staff making it difficult, despite their willingness, to secure an interview date and time. Inclusion and exclusion criteria are described in the next section.

4.4.7 Inclusion and exclusion criteria: practitioners

Inclusion criteria:

- Junior doctor, senior doctor, consultant or clinical nurse specialist
- Works within the haematology speciality
- Works at a hospital within the YHHN area

Exclusion criteria:

- Foundation year doctor or ward nurse
- Not working within a haematology speciality
- Not working at a hospital within the YHHN area

4.4.8 Practitioner sampling strategy

Sampling practitioners was predominantly purposive (as in the patient sampling strategy), the primary concern being to ensure practitioners had some experience of treating patients with CML. Furthermore, sampling by certain characteristics, in order to represent the total YHHN staff population, was not possible as the composition of each hospital haematology team was unknown prior to the interviews. These factors made the group suited to snowball sampling (Ritchie et al, 2003^a), which involves locating key individuals to interview who can in turn then suggest others of interest to interview from the sampling frame (Robson, 1993), so is a useful way of accessing hard to reach groups. This method relied on my ability to identify key individuals. In order to do this, I began by contacting the clinical nurse specialists who had responded and previously helped with the

recruitment of patients, which implied they had an interest and knowledge of the study. Senior research colleagues were also able to suggest practitioners who may have an interest in my thesis and I also knew some of the staff from my work as a study nurse on the wider YHHN registry within various hospitals. Following each interview I asked each practitioner if they could provide me with information about their hospital haematology team, and based on that, asked if they could suggest other people who may be interested in taking part in an interview.

Despite snowball sampling, I monitored the key features of the practitioners' role; their speciality in CML and the type of hospital they worked in. Speciality in CML was defined as either running CML specific services, such as a nurse led CML telephone clinic, or having a special interest in CML within their role, whereas generalists were not involved in any CML specific services and had a general interest across all haematological malignancies. I intended to recruit a practitioner from each hospital in the YHHN area but unfortunately, was unable to secure a participant at two hospitals which explains the lower than anticipated number of participants (n=13). Despite this, my supervisors and I considered that data saturation had been reached at the point of thirteen interviews as no new codes were added or new themes developed, also code and meaning saturation were achieved, as with the patient interviews (Hennink, Kaiser and Marconi, 2017)

Characteristics of the included practitioners and their diverse experiences are shown in the sampling grid; table 5. Practitioners who were interviewed are shown by their study code in bold, or in grey if they were contacted but did not respond or responded but unable to fit in an interview time and date. All practitioners were sent a standard email containing an invitation letter and information leaflet (see appendix 8 and 9). They were sent one or two reminders and if they did not respond, then I did not contact them again. Interviews were carried out between 20/02/2018 and 04/04/2019. Following interview, a thankyou letter containing YHHN and my own contact details was sent to practitioners.

Table 5: Practitioner sampling grid

	CML specialist	General haematology
Hospital with Cancer centre	PR01 CNS PR02 Consultant PR03 CNS PR14 CNS	PR16 Consultant PR20 Consultant
Local Hospital	PR05 CNS PR08 CNS	PA04 CNS PR06 Consultant PA07 Consultant PR09 Consultant PR10 Consultant PR11 Consultant PR12 CNS PR13 Consultant PR15 Consultant PR17 CNS PR18 Speciality Doctor PR19 CNS PR21 CNS

4.5 Interview schedules

The original patient and practitioner interview schedules, or topic guides, were based on the narrative literature review, qualitative synthesis, consultations with senior colleagues and meetings with two CML patients from a local haematological malignancy support group. Questions were open in order to enable participants to expand, and choose which areas of the topic they wanted to talk about (Barbour, 2014). As patient interviews were to be carried out first, I practiced the patient interview schedule with a senior research colleague acting as participant. This, together with talking to the support group patients acted as pilot interviews and enabled me to gain some confidence in myself as an interviewer. As a result of these pilot interviews, I found that patients naturally preferred to tell their story from diagnosis though treatments, to the current time. This informed a change to the patient schedule in that a question about the time of diagnosis was added, which I originally felt was not relevant for the thesis aim, however by not asking this, I was limiting the patients preference to talk in a way which put them at ease and narrate their story in a way that made sense to them.

Following initial patient and practitioner interviews, the schedules for each were revised in order to improve the sequence and wording of questions, a redrafting which is advised as being good practice (Braun and Clarke, 2013). For example, I realised after the initial practitioner interviews that I required more detail as to the context of their practice, so rather than asking simply about how they see CML patients in the context of their other patients, I also asked about how their outpatient care was set up in order to obtain a wider picture. I also re-sequenced questions at the initial part of the practitioner interview to begin with their professional details such as years qualified, role in haematology team, then moved onto features of outpatient care. Practitioner interviews tended to be more succinct and systematic in their responses, so responded well to these more factual questions at the beginning of the interview, and this provided time to build a rapport, create some ease and act as an entry to questions with more depth such as how they dealt with complex cases, and made difficult decisions. Final interview schedules are shown in appendix 10.

4.5.1 Qualitative interviewing

Using the interview schedule, I undertook semi-structured interviews with patients and practitioners. Semi-structured interviews involve a balance between the topics/questions I have set as the researcher, and allowing space and time for participants to express their perspective (Barbour, 2014). I found that initially, I viewed the interview schedule regularly, checking questions were asked, so sometimes asking questions which the participant had already covered. As I became more experienced, I was able to remember the questions so could note to myself when a participant had answered a question later on in the schedule and avoid asking it again, and the interview came across as a more natural conversation. This was particularly beneficial to patients, who preferred to express their narrative from diagnosis onwards rather than be drawn in to an order of topics. Experience also built my confidence in asking probing questions, to ensure I understood their answer and provide more detail and depth to their account, a crucial part of qualitative interviewing (Legard et al., 2003).

Participants were offered an interview at the University or a place of their choosing, with the intention that they would select a location where they felt comfortable (Braun and Clarke, 2013). Interviews with patients were undertaken in their own homes, although I provided alternative options. Sometimes pets were present and relatives sat in on the interview, or were in and out of the interview room. Practitioners were all interviewed at their place of work, all but one in a private office. However, due to the nature of their work, colleagues sometimes entered the room if it was a shared office or they came to discuss clinical work, and phone calls were sometimes answered.

Having worked as a district nurse I felt confident to manage these situations to minimise disruption to the recording whilst maintaining a sense of ease about the interview.

4.5.2 Recording and transcribing interviews

Interviews were all recorded onto a small digital recording device which was explained to participants at the start of the interview. All participants agreed to this, and although sometimes a little nervous, they seemed at ease with the process as the interview progressed. I took the decision not to take any notes in addition to the recording as this took my attention away from the conversation and would interrupt the dynamic of the interview (Britten, 2006). Recorded interviews were encrypted, uploaded onto an encrypted memory stick and given to a dedicated transcriber who then typed the interviews, taking care to remove any identifiable factors, such as hospital names. Interview transcripts were returned via the secure memory stick, then I checked through them and corrected any inaccuracies against the recording. This also formed an initial step in data analysis.

4.5.3 Confidentiality

Before the start of each interview, I took care to take time to introduce myself and the study, the interview process, and to explain the level of confidentiality maintained throughout the study. Participants also received a leaflet containing information on confidentiality prior to the interview (see appendices 9 and 11). A concern was raised at the Research Ethics Committee (REC) meeting, that a patient may disclose a dangerous level of non-adherence, in which case it was my duty of care to inform their practitioner. The following information was therefore added to the patient information leaflet; *“if we consider your health is at risk because of anything you tell us we will encourage you to contact your GP, hospital doctor or nurse and we reserve the right to do this for you”*. The REC also requested that the word ‘patient’ was replaced with ‘participant’ on their paperwork, however I refer to these interviewees as patients in this thesis, to distinguish them clearly from practitioners. Participants were asked to read through and sign a consent form prior to the interview beginning, of which they were provided with a copy as well as my contact details (see appendix 11). The patient consent included an agreement that I would contact their practitioner to make them aware they had been involved in the study. This was done via a standardised letter following the interview. Occasionally, in the patient interviews a relative was present. If they wished to be present during the interview process, I checked if the patient was happy with this. If so, the relative was present for my introduction, explanation of confidentiality and the consent process. These actions were taken to mean the relative also consented to being part of the interview, and it is likely their presence enhanced the data by providing a useful perspective and putting the patient at

ease. Each participant was provided with a code number, unique to this thesis, at the point they were identified for sampling. This was then used in all study paperwork and records. As stated earlier, any identifiable factors were removed from transcripts. Interview transcripts and recordings were kept securely in a locked cabinet and office, to be destroyed five years following the study ending.

4.6 Approach to analysis: Thematic analysis

My approach followed thematic analysis, as described by Braun and Clarke (2006, 2013), who note that their process is not “unique” to thematic analysis, but commonly used by many qualitative researchers despite their differing approaches. The process involves an identification of “patterns or meanings” in the data, which become themes. These themes are then described and their meaning explored later in the analysis (Braun and Clarke, 2006). As a novice researcher, having never coded or analysed qualitative data, I felt I needed to develop my skill in this area, for which Braun and Clarke’s (2013) book was immensely helpful. The authors emphasise that such skills can be developed, yet warned that whilst their guidance offers a method of producing systematic work, a need for analytical awareness remains. Furthermore, they stress the method is iterative, and that researchers must go back and forth during coding and analysis, a process I maintained and is described later (Braun and Clarke, 2006). A summary of thematic analysis as described by Braun and Clarke (2006) is shown below in figure 9.

Figure 9: Phases in thematic analysis from: Virginia Braun & Victoria Clarke (2006) Using thematic analysis in psychology, *Qualitative Research in Psychology*, 3:2, 77-101

1. Familiarizing yourself with your data
2. Generating initial codes
3. Searching for themes
4. Reviewing themes
5. Defining and naming themes
6. Producing the report

The next section describes how I worked through each stage. Although patient and practitioner interviews were analysed separately, a later chapter (chapter 8: contextual summary) merges these, comparing themes and offering explanations.

4.6.1 Familiarisation

The coding process began with a period of familiarisation with transcripts, which is suggested as an essential first step in data analysis (Braun and Clarke, 2006; Ritchie et al., 2003^b). Braun and Clarke

(2006) advise this stage provides a foundation for analysis as it ensures the researcher is aware of the complexity of the transcripts. Familiarisation involves reading and re-reading the interview whilst noting any thoughts about the data which seems significant (Nowell et al., 2017), which I did. I also kept a reflective diary, documenting my processes and any concerns, to bring to supervision.

4.6.2 Generating codes

The next step in thematic analysis is generating initial codes (Braun and Clarke, 2013). Coding is a process of describing characteristics of the text, in a word or phrase, which are of interest to the research question (Nowell et al., 2017; Braun and Clark, 2013). Care was taken at this point not to interpret the data, but only to apply word(s) or label(s), that can later be identified and used to generate themes and meaning (Pope, C., Ziebland, S. and Mays, N., 2006). This process is described by some authors as 'indexing' the data (Seal 1999, cited by Barbour, 2014). However, Braun and Clark (2013) also note that codes need to 'capture the essence' of why the text is important and warn against assigning codes which do not inform us of anything useful. Achieving a balance between generating codes which convey some of the meaning of the data without interpreting it was a difficult process and required thinking through different words or phrases for each code.

Thematic analysis employs 'complete coding', which Braun and Clarke (2013) describe as coding all text relevant to the research question. This contrasts with 'selective coding', often used in grounded theory or discourse analysis (Braun and Clarke 2013; Pope, C., Ziebland, S. and Mays, N., 2006), where only text relating to certain topics is coded, so data are condensed to that of relevance to certain areas. Complete coding applies equal attention to all the data (Braun and Clark, 2006) and was suited to the broad aims of this thesis. Codes were written on the interview transcript in the right hand margin. Braun and Clarke (2013) describe further aspects of coding, including 'data-derived' codes and 'researcher-derived codes'. 'Data derived codes' directly reflect the participant's text and 'researcher-derived codes' involve the researcher adding a code which was implied from the participants' text rather than an explicit description of the text. For example, the practitioner code '*advice at diagnosis*' and its sub-codes which described aspects of advice such as reassurance and information, reflected what the practitioner was telling me, so is data derived. In contrast, some of the sub-codes within the code '*differences in practice between hospitals*' included '*CML specific clinic*' and '*sees mostly outpatients only*', were researcher derived, because the practitioner was discussing their individual practice, not commenting on differing hospital practices.

Initial coding

Several codes were identified from complete coding of the transcripts, and needed to be organised in a way which would facilitate subsequent searching for themes. Barbour (2014) describes the process of ordering codes in a meaningful way as the development of a 'coding frame'. I began by coding the patient transcripts and as a novice to the process of coding, I used the first three to test not only different ways of managing the codes but to try different wording for the codes. After familiarising myself with transcripts and noting my initial thoughts in the left hand margin I set about coding by underlining text and writing a code in the right hand margin (see appendix 12 excerpt of annotated transcript). I then hand wrote, then typed, the codes under headings onto paper, noting the line number supporting the line of code in the transcript. This highlighted that my coding was at a very descriptive stage. Several codes were based on interview topics, such as '*diagnosis*' and '*hospital care*' and lacked information about what the data were saying, such as whether hospital care was good or bad and what the experience of diagnosis entailed. Other codes were unique to individual transcripts, such as '*death of wife*' and '*anxiety about prognosis*'.

It became clear that the transcripts were coded individually with little consideration of how the codes from each interview may merge with each other. I therefore returned to the first two transcripts and tried to think more laterally across these about the text I had identified for coding, placing them under new or modified codes that said more about the data rather than just labelling them with the title of an interview question or a label individual to that participant. From this process, I created a single coding frame which was used for the third interview, with some additions. Although I felt the codes were still quite descriptive, this gave me the foundation of the coding frame I used throughout the rest of the interview analysis and I used this same process to build the practitioner transcript coding frame. As a final note, although the research aim was broad, the motivation of the study was pragmatic, to be of use to practitioners, therefore codes were derived with this in mind, for example patient codes regarding the management of side-effects were described as being "*managed independently*" or "*managed with professional advice*".

Use of NVivo

Examining the first three patient transcripts highlighted the importance of monitoring where the text supporting each code was located in the transcript. This had been done by writing transcript line numbers by the side of codes for each, however the transcript then needed to be hand-searched to find the actual text at that line number, which was cumbersome and time consuming. By using the NVivo analysis software (versions 11 and 12), as in the thematic synthesis, a code could be selected, which would collect all the text from each transcript where this code was applied, and show it in one

screen, noting which transcript the text came from. The patient and practitioner interview transcripts were uploaded onto NVivo following hand coding on paper transcript and adding to the coding frame on a word document. Although initially time consuming, once this process was completed, it saved time. I intended to create themes and links myself rather than using NVivo in some way to assist with this. Authors argue that although software packages may promote analysis via sorting, retrieving and sometimes making links between data, the researcher must direct the interpretation and hypothesising about the data (Braun and Clarke, 2013; Silverman, 2010; Pope, C., Ziebland, S. and Mays, N., 2006).

Subsequent coding

As each transcript was coded by hand, new codes were added to the patient coding frame in italics and saved in date order to track any changes if needed. It soon became clear, however, that extra 'sub-code' categories, called 'child nodes' in NVivo, were necessary to avoid an unwieldy list of codes. For example, under the patient code '*lack of disease knowledge*', sub-codes were added describing areas where the patient's knowledge was implied to be 'lacking' such as '*optimal dosing*' and '*treatment milestones*'. See figure 10 for an example of this early coding.

Figure 10 Example of early coding (patient interviews)

<p>Code: Lack of disease knowledge Sub-codes:</p> <ul style="list-style-type: none">• Disease monitoring• Second generation TKIs• Generic imatinib• Stopping TKIs• Treatment side-effects• Missing medications• Disease cure• <i>Optimal dosing</i>• <i>Treatment milestones</i> <p>Code: Good disease knowledge Sub-codes:</p> <ul style="list-style-type: none">• Drug history• Chronic presentation• Disease process• Prognosis• Disease monitoring• Hospital processes• Treatment• Co-morbidities

Around halfway into coding the transcripts, I began to take an overview of the codes, their meaning and any potential overlap. Using NVivo, I could print off the text for codes which appeared to overlap and look at either merging or defining the codes further. For example, text within four codes from the practitioner transcripts had some overlap in their meaning; *'awareness of side-effects'*, *'lack of awareness of side-effects'* *'active management of side-effects'* and *'patient motivation to report side-effects'*. After re-reading the text for each code, the text for *'awareness of side-effects'* and *'lack of awareness of side-effects'* could all be re-coded into the other two codes and these codes removed. See figure 11 for this example of early coding.

Figure 11 Example of early coding (practitioner interviews)

Code: Patients motivation to report side-effects
Sub-codes:

- Don't want to bother doctor
- See it as low level or manageable side effect
- Waited too long in clinic
- Reports to CNS
- Reports to GP

Code: Active management of side-effects
Sub-codes:

- Medical management
- Communication
- Age and co-morbidity
- Awareness of SEs
- Information and awareness
- GP's job
- Switching TKI

To be clear on how codes were different I compiled a list of definitions to be followed on subsequent coding. For example, the patient code *'wants or seeks advice, support and information'* was defined as the patient describing what someone told them about their disease, stating they wanted to know something, or asking me questions about the disease, whereas the similar code; *'good disease knowledge'* was applied when the patient could explain something about the disease, as the 'owner' of this knowledge. The process of reviewing codes was repeated for each patient and practitioner transcript, and notes kept.

After the last patient and practitioner transcripts were coded, the coding frame was examined to check if further sub-code/code merging was possible. Using NVivo, when changing code names and merging codes, the attached text could easily be moved with them, and paper notes were also kept

of how codes were changed. The final coding frames contained 72 patient codes and 57 practitioner codes, with several more sub-codes (see appendices 15 and 16 final patient and practitioner transcript coding frames). These codes were split between headings, as follows; patient transcripts: *CML perspective over time, advice and understanding, treatment, managing medication, co-morbidity, health care service/professionals and quality of life*; practitioner transcripts: *clinical practice/set up, quality of life/side-effects, advice, adherence*. Evolution of the coding frames through checking and re-checking codes and text represents an iterative process widely recommended by qualitative authors (Barbour, 2014; Braun and Clarke, 2013; Pope, C., Ziebland, S. and Mays, N., 2006). The final coding frame was reviewed by a senior research colleague alongside three randomly chosen interview transcripts. We then met and discussed the coding and reached a consensus that this final list adequately represented the transcripts. This supported the reliability of the analysis, which is described in more detail later in this chapter.

4.6.3 Searching for themes

As with the qualitative synthesis, coding frames were developed for each set of transcripts, comprising of codes under overarching headings. At this point codes were grouped together based on a similar literal meaning, often sharing similar wording. For example, the patient heading *'treatment'* contained the codes *'side-effects'*, *'no side-effects to TKIs'*, *'managing side-effects independently'* and *'side-effects impact on missed medications'*. Although these share some literal meaning describing aspects of taking treatment, I not only wanted to explore the CML experience but to look further into the data to provide links between codes or explanations which would address the final research aim; to provide practitioners with evidence which is relevant to clinical practice. Therefore, *'side-effects'* and *'no side-effects to TKIs'* were placed under the sub-theme: *'treatment success and side-effects'*, and *'managing side-effects independently'* and *'side-effects impact on missed medications'* were placed within the theme: *'managing the disease is individual'*. This reflected more of the meaning in what the patients said and presents the data in a way which is helpful to practitioners. It follows Braun and Clarke's description of a theme as:

“...something important about the data in relation to the research question, and represents some level of patterned response or meaning within the dataset.” (Braun and Clarke, 2006)

Similar to the thematic synthesis method, prior to moving the codes under the newly defined themes and sub-themes, they were colour coded according to their appropriate theme so I could 'track' the codes. See figure 12 for example of allocating codes under themes.

Figure 12: Allocating codes to themes: practitioner interviews

<p>Heading: Quality of life/side-effects</p> <p>Sample of codes (colour coded by theme):</p> <p>CML doesn't/ has little impact on daily life</p> <p>QOL unclear link with molecular response</p> <p>CML impact</p> <p>Patient perspective</p> <p>Socioeconomic gap in survival reasons or why do some people do better than others</p> <p>TKIs are well tolerated/ side-effects rare</p> <p>TKIs are not always tolerated</p> <p>Side-effects do occur</p> <p>Side-effects or symptoms complicated by co-morbidity</p> <p>Co-morbidity does not complicate treatment</p> <p>Side-effects complicated by social/psychological issues</p> <p>Treatment complicated by co-morbidity</p> <p>Patient motivation to report side-effects</p> <p>Poor management of side-effects</p> <p>Active management of side-effects</p> <p>Patient management of side-effects</p> <p>Side-effects – patients have to live with them</p> <p>Themes:</p> <p>IMPACT OF CML AND ITS TREATMENT</p> <p>WIDER INFLUENCES ON CML MANAGEMENT</p> <p>MANAGEMENT OF CML AND ITS TREATMENT</p>

4.6.4 Reviewing themes

As part of the final analytical steps, theme headings were checked by returning to the transcripts and individual coded data, using NVIVO, to consider if data within each theme provided a robust case for its definition. For example, re-examination of the patient codes '*pre-diagnosis delay*' and '*prompt diagnosis*' showed some patient transcripts had data in both codes. By looking at this coded data I could consider the reasons why the same person described diagnostic delay as well as prompt treatment. For example, one of the reasons for reporting diagnostic delay was participants blaming themselves for not seeking GP input sooner, however they were also satisfied that once referred to hospital, diagnosis from this point was prompt. This was incorporated into the text of the interview analysis chapter.

This stage also involved returning to the patient interview transcripts as a whole. Braun and Clarke (2013) suggest the aim of this step is to ensure analytical themes encapsulate the "meaning and spirit of the dataset". A sample of each set of transcripts were read in their entirety and notes made to check that aspects of the data that seemed to carry the salient messages in the transcript had

been coded and included in an analytical theme. I also wrote down what I believed was the strongest message from each interview such as, from patient interviews; 'making sense of diagnosis: comparing to sick mother', or 'side-effects, shortness of breath, dominate', and checked this against codes and themes. While this resulted in some changes, I found that most of the notes and salient messages were adequately coded and included within the analytical themes.

4.6.5 Defining themes

The definition of analytical themes followed the process described by Braun and Clarke (2006, 2013), which advised that themes include several concepts related to a "central organising theme", thereby differing from a code, which describes only one idea (Braun and Clarke, 2013). However, I found that the final theme titles acted both to define the theme and as a central organising concept, and that trying to 'add in' a further central organising concept became unnecessary and confusing so I decided not to omit this. Themes should also define a feature of the data rather than being purely descriptive, as the latter does not provide any deeper understanding of the data (Braun and Clarke, 2013). For example, if the overarching practitioner heading '*quality of life/side-effects*' was used as a theme title it would merely describe aspects of quality of life and define side-effects, without information about how this impacts on the patient experience. Codes from this heading were eventually placed under a theme titled '*impact of CML and its treatment*' which helped to link aspects of disease and treatment to their impact on daily life.

Braun and Clarke (2006) explain that the patterning or size of a theme relies to an extent on the number of times a response is seen in the transcript, but also whether the theme is 'key' in its ability to explain a concept of importance to the research question (Braun and Clarke, 2006). Morse (2015) describes similar concepts of 'replication', where data from different participants is similar, and 'scope' meaning the completeness and 'depth' of the data. Morse (2015) argues that without these features, theory generation is problematic. For example, the overarching patient heading '*quality of life*' contained several reports from patients referring to the benefit of support from family and friends, and the different ways this helped. However, merely describing the support of family and friends under a theme named '*quality of life*' would disregard the wealth of data patients recounted about features of social support, which explained its importance to them, in other words it would disregard the 'depth' of the data. By 'removing' the codes related to the support of family and friends from the '*quality of life*' heading and defining a theme around them: "*Social support: level and type matters*", allowed this support to be examined more closely, and to consider how the quality of support affects how patients manage their disease.

In order to implement the changes described above, and generate analytical themes, visual mapping was used (as in the qualitative synthesis). Braun and Clarke (2013) advise this as a good way of ‘exploring’ the data in order to define themes. This involved printing each individual code so I could view it without seeing its overarching heading and associated codes, and gave me the freedom to move the codes around in relation to the research aims.

The steps described in this section (searching, reviewing, defining themes) in fact ran alongside each other and resulted in the final analytical themes and subthemes. Five themes were defined from the patient interview analysis: *significant impact of disease, social support and type matters, hospital care: good and bad, personal influence* and *managing the disease is individual*. The practitioner interview analysis resulted in four analytical themes: *clinical practice differs, impact of CML and its treatment, wider influences on CML management* and *management of CML and its treatment*. Some of these themes contained sub-themes. Within each theme or sub-theme headings were sometimes used as a way of organising the large amount of interview data. For example, under the practitioner theme *clinical practice differs*, was the sub-theme *clinical decision making influences* and within this were four headings to organise the data such as *guidelines and clinical trials*.

4.6.6 Producing the report

As with the thematic synthesis, I chose to write the analysis of patient and practitioner findings “illustratively”, rather than “analytically” (Braun and Clarke, 2013). Although more descriptive, my account of the findings used illustrative sections of the transcript to provide rich description of the themes. As in the thematic synthesis, where a quotation specifies “...” this indicates some text has been removed which isn’t relevant to the issue of interest. Where a quotation specifies “[text]” I have added a word(s) to help explain the quotation. In some interviews where a relative was present and had added dialogue, this was marked as “*relative*” in front of the quotation.

I have presented each theme, and its sub-themes in order to “tell a story” about the transcripts which links themes and provides validity to the account (Braun and Clarke, 2006). In addition I have created a visual map showing the themes from each set of interviews and demonstrating links identified as part of the analysis. This provided a useful “alternative view” of the themes (Braun and Clarke, 2013). As a novice researcher this approach was fitting as I benefited from starting with a descriptive account, before moving to a more analytical approach. The contextual summary chapter (chapter 8) presents a more analytical account by comparing the themes from the patient and practitioner findings and offering explanations for differences and similarities, linking to wider literature to validate themes and offer explanations. In the final section of this current chapter I review issues of methodological quality.

4.7 Wider application of findings and qualitative rigour

It is generally accepted that the quality, or rigour, of qualitative research should be appraised (Long and Johnson, 2000). Notions of reliability and validity, their meaning and appropriateness as a measure of rigour continue to be debated in qualitative research. These concepts are more aligned with ensuring rigour in quantitative measures, whereas in qualitative research findings are focused on investigating a phenomena from the perspective of different individuals and their contexts, so as such cannot be objectively measured (Maher et al., 2018). Rigour in qualitative research uses more appropriate methods to ensure confidence in study findings, and Lincoln and Guba's model of trustworthiness is often cited in order to guide the judgment of this (Lincoln and Guba, 1985). The four elements from this model are now considered with regard to the qualitative investigation in this thesis.

4.7.1 Transferability

Transferability describes the ability of the research findings to be applicable to another setting or context (Maher et al., 2018; Thomas and Magilvy, 2011). This thesis used different strategies in order to generate transferable findings. As discussed, the patient sampling strategy aimed to produce representational generalisability through purposive sampling by age at diagnosis, gender and hospital type, to ensure that the characteristics of the wider YHHN CML population were reflected. This contrasts with a quantitative sampling strategy, which aims to provide statistical inferences that are applicable to a wider population (Lewis and Ritchie, 2003). Representational generalisability was also attempted among practitioners, by hospital type and specialism. However due to the sampling method, as well as unknown aspects of the total practitioner sample, it is uncertain if a representational sample would, or could, have been achieved, although characteristics of participants were recorded, in order to describe the sample.

Guba and Lincoln (1982) describe transferability as the ability of findings to be transferred to other contexts (Flick, 2014) and it is argued that by providing "rich description" of research analysis and context, other researchers can judge if the findings are transferable to different settings (Lewis and Ritchie, 2003). Flick (2014) adds that the degree of intended transferability should be specified by the researchers. To this end, I have provided a detailed description of the thematic analysis process and have written my findings in a way that provides context regarding individuals, with sufficient and relevant participant quotations to support the analysis.

4.7.2 Credibility

Credibility describes the extent to which the research findings reflect the reality of those participating in the study (Maher et al., 2018, Thomas and Magilvy, 2011). One way I attempted to enhance credibility was by the prolonged and thorough analysis of participant data, looking for similarities and differences between and within individuals. My entire approach to data analysis was iterative, involving checking and re-checking my understanding of codes, themes and supporting evidence; and keeping a diary to document coding processes and interview observations. Member checking is a further technique used to support credibility in the thesis. However, a decision was made not to carry this out by asking all patient participants to comment on findings, to avoid problems of reluctance or feeling of pressure to participate, which seemed unfair following a single interview and short-term relationship with myself and the study. Furthermore, practitioners were not asked to review a summary of my findings due to the NHS dealing with the coronavirus pandemic. Instead, I planned to ask two patients with CML from a local haematological malignancy support group, who helped develop the interview schedule, and were likely to have an ongoing interest in haematological malignancy research. Unfortunately, one patient was unwell at the time I requested feedback, but useful responses were received from the second patient who considered how the study findings reflected their experience of CML, and this expert consultation is incorporated into the summary and discussion chapters (see sections 8.3.2 and 9.6). The patient's feedback is listed below in figure 13 under the appropriate patient analytical theme. Each piece of text is followed by a tick (✓) to represent that the patient agreed with the patient interview analysis theme, or **NEW** to indicate a response not seen in the patient interviews.

Figure 13: Expert consultation

Theme 1 : Significant impact of disease

Ongoing side-effects: muscle cramps (well controlled with medication) ✓

GI symptoms: stress related (consultant opinion) ✓

Low Hb: highlighted early on and followed up by drugs company and consultant. Drug company felt not related to imatinib, advised to take with water, then food. **NEW**

Agrees with reluctance to take more drugs for side-effects (related to recurring anaemia and iron tablets) ✓

Theme 2: Social support and level matters

Life events: stress related to family events, “overtook” life for some time, consultant felt GI symptoms related to this. ✓

Lucky with family support ✓

Theme 3: Hospital care: good and bad

Nature of staff: Good relationship with current consultant and overall medical treatment good/excellent ✓

Health system: hospital admin problems: main “side effect” for patient – “poor”: ✓ and **NEW**

Pharmacy: (probably other patients/diseases also: refers to patient group member) change from hospital pharmacy to in house private arrangement (has since changed hands and now working very well) – negative experience: only issued 1 months’ supply previously was 3 months (against consultant instruction), started to deliver to local pharmacies then stopped this without full explanation, almost out of date drugs issued (previously had at least 18 months left), medication left on shelf without informing patient it was there. Effected many patients and was taken up with the pharmacy by haematology department ✓ and **NEW**

Continuity: Now has a regular consultant but prior to this had appointment in specific consultant’s clinic but when was routinely in another hospital ✓

Patient letters: Hospital uses a private mail company with royal mail delivery, this means letters take up to 7 days to arrive and events can overtake letters **NEW**

Outreach clinic: works well, efficient, friendly, helpful. Thinks not widely used by their hospital. **NEW**

Stopping TKIs: took over a year to start this due to slow admin **NEW**

Theme 4 : Personal influences

Perspective on life

Feels lucky due to family support, information, treatment, very good disease response and ability to immerse self in data, but “*even so, it has not been easy*” ✓

Disease knowledge and awareness varies

Stopping TKIs: tried a reduction in dose which was unsuccessful. Suspects that full dose alternate days may work better **NEW**

CML support website: useful sometimes, and annual conference also helpful update ✓

Is able to immerse self in data/info **NEW**

Theme 5: Managing the disease is individual (adherence and side-effects)

Thinks adherence could be related to socioeconomic background, also points out Covid immunisation information difficult to understand **NEW**

Adherence: Has missed the odd dose, usually due to change in routine, sometimes GI symptoms ✓

Response is good (MR4.5 ongoing) ✓

Managing side-effects with professional advice: Has discussed side-effects with current consultant: prescribed medication, discussed stress, liaised with drug company, further investigations ✓ and **NEW**

Triangulation is a further method employed in this thesis to ensure credibility, and involves the use of different data collection sources or methods to ensure the phenomena explored is accurately described (Braun and Clarke, 2013; Mays and Pope, 2006). In this thesis, two data sources (patients and practitioners) were included and themes compared for similarities and differences (see chapter 8). In addition, findings from the thematic synthesis and wider literature review are considered in the summary and discussion chapters (chapters 8 and 9) with respect to the themes identified from the interview analysis. It is anticipated that these data sources may not fully corroborate each other, and I attempt to provide a rationale where I understand this to result from source validity or merely different perspectives on the CML experience.

An account of researcher reflexivity is also said to enhance study credibility including detail of the researchers' background, personal and intellectual characteristics, as these may influence the research (Mays and Pope, 2006). To fulfil this criteria, I can report that I am female and was aged in my mid-forties at the time the interviews were conducted. This means I am younger than the median age of CML diagnosis, and although well into my working life, I am carrying out this thesis as a student. Therefore there was potential for some "distance" between myself and the participants. I attempted to minimise this by clearly describing the study, my role and the wider YHHN team, to maximise interviewee confidence in me. Also, I have a professional background having worked as a clinical nurse for many years, fourteen of which were within the NHS. I have enhanced my awareness of theoretical approaches to qualitative study during this thesis, and understand the importance of knowing how this relates to research questions and study design. I believe that my clinical experience led me to pursue research that is pragmatic and can contribute to the planning and provision of care. Finally, this chapter clarifies and justifies my methodological and analytical approach, along with outlining the decision making required to operationalise my research question. This ensures my account is transparent and therefore consistent with the general principles of reflexivity, an approach which will continue throughout the thesis.

4.7.3 Dependability

The notion of dependability refers to the ability of the research process to be followed by another researcher (Thomas and Magilvy, 2011). To this end, a detailed description of the methodology has been documented in this chapter including examples of how data was coded and themes derived. In addition, a senior research colleague was asked to check the coding of the thematic analysis and a selection of participant interviews. They were asked to consider if the coding was appropriate and any discrepancies were discussed and revised where necessary (Mays and Pope, 2006). The sampling strategy, as described, was intended to enhance dependability, as was a consistent approach to each interview (introductions, study explanation, timing etc), and a systematic analytical process, supported by adequate interview evidence (quotations) (Lewis and Ritchie, 2003)

4.7.4 Confirmability

I believe that this thesis maintained confirmability in that I took steps to enhance transferability, credibility and dependability (Thomas and Magilvy, 2011). As described, I maintained an iterative and reflexive approach throughout data collection and analysis. I achieved this through completing a reflective journal following each interview and detailed note taking on each step of the analysis process. By making and justifying changes to my approach and analysis, and offering the account of reflexivity in this section, I hope to have demonstrated a critical approach.

4.8 Summary

This chapter has detailed both the research techniques used in the thesis, and a consideration of the generalisability, reliability and validity of the research design. My research questions are amenable to an interpretive approach that can incorporate pragmatic findings: this is reflected in “subtle realism” believing a shared and negotiated reality can be known through individuals’ accounts, which can be used to produce evidence for practice. Qualitative research is well suited to this thesis, and various traditions were considered. Thematic analysis was chosen due to its suitability to broad research aims and commitment to transparency through its excellent guidance, which also enhanced methodological rigour. There were elements of other approaches which, on reflection, may have improved this thesis, including ethnographic observation of CML outpatient clinics, which were the main setting for patient/practitioner interaction, and may have deepened my understanding of the similarities and differences in the patient and practitioner interviews (for example, accounts of advice given at diagnosis). Also, the use of grounded theory may have enabled theory to develop as the study progressed and informed later interviews. For example, there were instances in the analysis stage where I would have liked more data, such as how patients’ adherence changed over

time. By using a grounded theory approach I would have been forced to stop and review emerging theory at organised stages and this may have led me to incorporate new interview questions. However, thematic analysis lent itself well to my aims and taught me “how to” analyse qualitative data in a way that was consistent with the research question.

I have provided an account of my analytical process to support the credibility and dependability of my study, and have also incorporated additional techniques to enhance rigour, including the transferability of findings to the larger YHHN CML patient population. I have also considered my personal position with respect to data collection and the interpretation of findings. The underlying purpose of this chapter was to make clear my decisions as the basis for methodological rigour. The following chapters operationalise this and provide illustrative accounts of both patient and practitioner experiences. Next, the summary and discussion chapters locate findings within wider literature and theory, the summary chapter compares and contrasts major themes from the patient and practitioner interview analysis, and the discussion chapter relates findings to policy and practice.

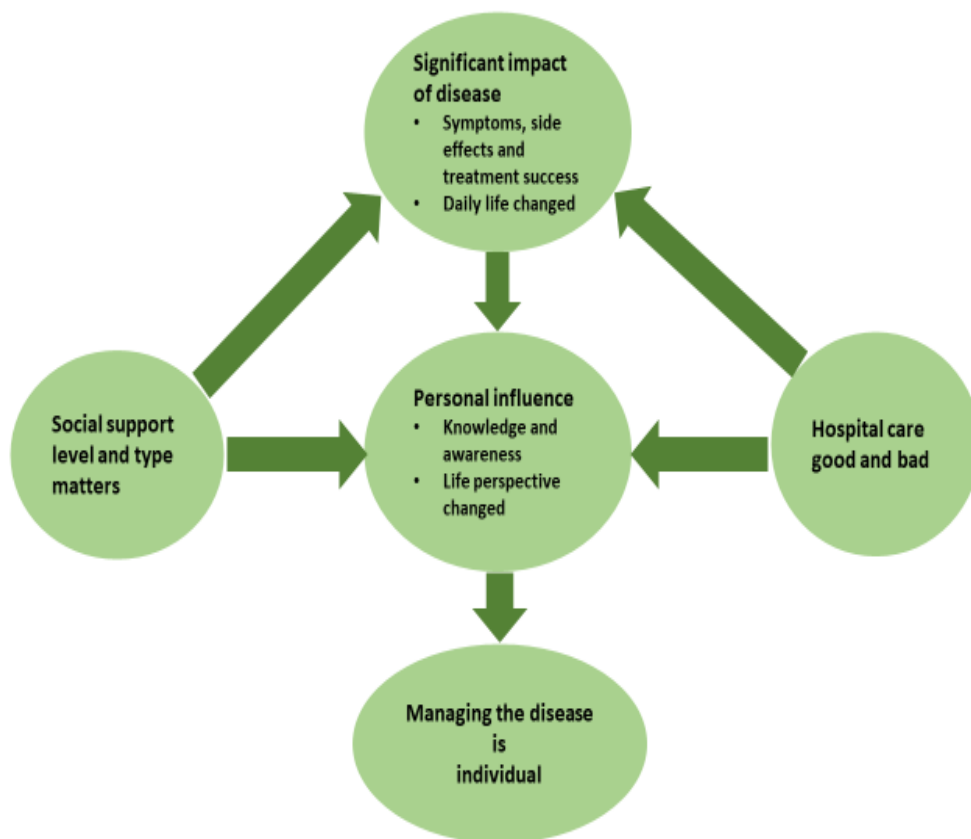
Chapter 5 Findings: patient interviews

One of the aims of this thesis was to explore the patient experience of managing treatment and living with CML. This chapter describes the qualitative patient interview analysis findings and attempts to do this in a way which is relevant to practitioners and to inform practice. Thematic analysis resulted in five main themes; defined from the final coding frame and shown in the visual map (figure 14). These are: *'significant impact of disease'*, *'social support level and type matters'*, *'hospital care: good and bad'*, *'personal influence'* and *'managing the disease is individual'*.

The visual map demonstrates the relationship between themes. The first, *"significant impact of disease"* describes how CML may have considerable impact on daily life despite it being considered a chronic 'low key' cancer by some. I suggest this impact can be moderated by the influence of the next two themes *"social support level and type matters"* and *"hospital care: good and bad"*.

Together, social support and hospital care can offer both a protective affect over the impact of disease and influence the fourth theme, *"personal influence"*, which explores individual differences in disease understanding and perspective on life. All four themes influence the final theme: *"managing the disease is individual"*, which describes how patients manage medication adherence and treatment side-effects; and reflects on aspects of disease management that are more amenable to change by practitioners. Relationships are presented as uni-directional as this is my interpretation of the findings, some further discussion of these relationships is offered alongside other literature in chapters 8 and 9. However, it is important to note that the relationship between themes may also be bi-directional, for example whilst the level of social support may buffer the impact of CML, in turn the impact of CML, such as giving up employment, may impact on members of the patients social support network. As outlined in my methodology, my approach is contextual. This explains my concern to explore the patient's experience in such detail so to enable the reader to understand their complex, nuanced and sometimes contradictory accounts.

Figure 14: Patient interview analytical themes



As noted in the methodology chapter (section 4.4.4 patient sampling strategy), seventeen patients were interviewed in their homes between 18/07/16 to 10/03/17, and were broadly representative of the total YHHN CML patient population in terms of age at diagnosis, gender and care setting (section 4.4.4 patient sampling strategy, table 4). Individual patient characteristics are shown in table 6. Where a characteristic is “not known” this is because the patient was identified via local CNSs using strategic sampling, rather than the patient being eligible for YHHN (section 4.4.4 patient sampling strategy).

Table 6: Individual patient characteristics

Study ID	Diagnostic hospital	Age at diagnosis	Gender	Date of diagnosis
PA02	CC	64	M	22/01/09
PA04	LH	69	F	03/11/08
PA06	CC	53	F	08/11/10
PA07	LH	56	M	02/03/15
PA11	CC	67	M	09/02/16
PA15	LH	52	M	18/02/11
PA19	LH	61	M	10/05/16
PA20	LH	52	F	05/04/16
PA21	LH	52	F	22/12/15
PA24	CC	38	M	24/11/06
PA25	CC	55	F	14/05/12
PA26	CC	66	F	09/07/04
PA27	CC	Not known	M	Not known: <2004
PA28	LH	77	M	28/07/11
PA29	LH	Not known	F	?10/05/02
PA30	LH	44	F	12/11/08
PA32	LH	43	M	24/03/14

Abbreviations:

Hospital with cancer centre: CC

Local hospital: LH

5.1 Theme 1: Significant impact of disease

This first theme introduces the disease experience by describing the many side-effects and variable success of treatment, and ultimately how the disease and treatment impact on normal day to day living. The theme is mainly a descriptive account, providing background understanding about the disease impact before progressing to more analytical themes.

5.1.1 Sub-theme 1: Symptoms, side-effects and varying treatment success

Pre-diagnosis symptoms

Almost all patients reported symptoms pre-diagnosis, which were often non-specific and had not led the patient to suspect a serious illness. Patients frequently reported feeling unwell, tired, losing weight or experiencing sweats:

“I was feeling really tired. Didn’t really want to do anything, I’ve got two dogs that I walk twice a day and I didn’t want to do anything like that. I felt really run down.”

(PA15)

Less common side-effects included abdominal lump, infections, shortness of breath, priapism, lack of sleep, indigestion and dizziness. The majority of patients described a prompt diagnosis and treatment start. Often this was described in positive terms, complementing the hospital service on their efficiency:

“They sent me straightaway to the hospital. I was dealt with amazingly, the treatment I had was absolutely superb. Within the week I was diagnosed and then it went from there.” (PA04)

Several patients reported that the time from seeing their GP to attending hospital or being diagnosed was a matter of days and the process of diagnosis was also described as efficient, taking less than a week. Despite these positive reports a small number of patients recounted delayed GP referral to hospital. PA29 and PA30, who spoke highly of their current and regular GPs, expressed concerns about other GPs in the practice in relation to their diagnosis. PA29 described a GP who was unwilling to take routine blood samples and delayed acting on her symptoms for some months, although she described her spleen as being clearly enlarged. PA30 was unwell, breathless, had very sensitive skin, weight loss and problems hearing. The GP advised her she had a virus and provided her with an inhaler. PA30 responded by taking paracetamol and presuming she would improve. However, at an opticians appointment soon after, haemorrhaging in her eyes secondary to her CML was picked up and the optician referred her to hospital:

"I had all the classic symptoms...unfortunately I saw a, which is fine they've got to learn, a trainee doctor, a locum doctor but the other doctor that I saw who I saw who I don't particularly see now because I don't trust him, was an experienced doctor and should have picked it up." (PA30)

Several of the same patients who reported prompt diagnosis also talked about delayed diagnosis or treatment. This contradiction was usually due to patients regarding themselves as delaying their initial diagnosis due to them ignoring early symptoms and not seeing their GP:

"I had lost a drastic amount of weight but I didn't realise it until the point where my uniform was, and my trousers were sliding off me and when I look back on photographs, why didn't I recognise it? But you don't." (PA25)

Reasons for treatment delay included a patient who requested this due to the Christmas period, and fears of starting treatment based on her experience of caring for her mother, who had a different cancer:

"The doctor said, you know, the specialist he said they'd be no problem on that, you know, so I actually started in the January with the treatment." (PA06)

Another patient experienced treatment delay due to awaiting a funding request for imatinib, a new treatment at the time (PA29):

"...it went to the board and it was whether they'd fund it for me and there was a wait and my consultant was, you know, at the time she was worrying and we were all worrying." (PA29)

Success of treatment

Many patients reported currently receiving successful treatment, several remaining on the same tablet since diagnosis, although some had switched medication. Patients most commonly referred to measures of success in terms of treatment being '*fine*' or '*good*', but also in numbers or percentages, presumably referring to the BCR-ABL level on molecular monitoring, with varying accuracy. Some also discussed seeing the '*graph*' and being in the '*green*' as a positive sign regarding response:

“Yeah these are marvellous you know. Like I say they’ve fetched me down into the green, just into the green section so it’s obviously controlling it, you know.” (PA07)

Understanding that their disease was responding well helped patients to accept their diagnosis and continue with day to day life, which is explored in more detail in *theme 4 (sub-theme 2 perspective on life is changed)*. Several had also experienced treatment failure either due to an inadequate response or side-effects which led to a change in medication or dose reduction. Commonly, patients referred to this as the drug as ‘not working’ or results ‘going up’ when the response was sub optimal. How patients understood their treatment response is explored further in *theme 4 (sub-theme 1 knowledge and awareness varies)*:

“Yeah because the Glivec stopped working they put me on this, this Tasigna.” (PA07)

Some patients experienced a switch of drug and/or dose reduction due to side-effects. These were mostly described in serious terms including pleural effusion, severe allergic reaction and continuous nausea. PA29 had been taking imatinib for many years and had experienced side-effects, but declined the offer to switch to a different drug, due to uncertainty about its benefits and side-effects, and if they could return to imatinib if the new drug failed. Notably, these changes were all made on the advice of hospital doctors bar one patient (PA24) who decided to reduce their medication dose due to significant fatigue. This was on the advice of their alternative therapist and PA24 did not inform the hospital team for some time, which is referred to in more detail in later themes. A further patient (PA21), who followed their doctors’ advice to reduce their imatinib dose due to side-effects, regarded her response as good. However according to ELN guidelines it was not optimal and she had missed first year response milestones. Again, this case is discussed further in later themes:

“I was getting diarrhoea and sickness, nausea all the time, headaches with it. So when I got back in touch with Dr [consultants name] down at [hospital name] he put me on an easier dosage not as strong.” (PA07)

Side-effects

Most of the patient group reported side-effects from their TKIs indicating the majority were living with some kind of consequence from their medication. Occasionally, it wasn’t clear whether these were due to the disease or the TKIs, however the effect remained the same. Some related side-effects to the time of diagnosis and start of treatment only, whereas others were currently

experiencing symptoms. Gastrointestinal problems were commonly reported, including nausea, vomiting and diarrhoea.

"I've had to stop the car a few times going into work and throw up. But then I could have a few weeks and I wouldn't be sick, so there was no pattern to it." (PA30)

"I have it at breakfast time and I sandwich it within my breakfast. I can be sick after it if I don't." (PA04)

Equally common were problems with muscle pain or cramps:

"I used to get really bad cramps so they give me, I think it was like quinine or something like that to stop the cramps." (PA24)

"The tablet I think is, when I get the cramps in my legs and my arms, that is, and that can be bad sometimes, you know." (PA15)

Several patients also described fatigue, all of whom had ongoing and current problems with this symptom:

"The fatigue is the worst thing with both drugs and that varies day by day and it all depends on what I've done." (PA25)

Respiratory problems were reported by some, often pleural effusions:

"Like an effusion, pleural effusion, yeah that's the word. I had to go to hospital and it was like a membrane...I do get a little bit out of breath yeah. I was never like that before so it has affected me." (PA27)

Others discussed skin and hair effects, including changes to the hair, mouth ulcers, rash and sensitivity to the cold:

"...think this is a side-effect actually, cold sores. Well I got one on my eye while I was in there due to being run down and stress and that and to be fair I still struggle a little bit now." (PA24)

Varied cardiovascular effects were reported by a few patients including: an abnormal heart rate, raised blood pressure, stroke (although it wasn't clear if this was related to TKIs), and PA28 who was admitted to hospital with a pericardial effusion:

"The pericardial sac around the heart had filled up with water and it was squeezing my heart, but by some miracle, I think that was a Sunday, there was one of the top surgeons in Britain coming round the hospital." (PA28)

Less frequent symptoms included a lowered immune system, dizziness, tinnitus, allergy, mood change and blurred vision. Management of side-effects by practitioners and patients is explored in later themes.

The effects of CML were discussed alongside the effects of other co-morbidities. Side-effects could interact with other co-morbidities or confuse symptoms. A few patients described how their pain and fatigue had been exacerbated by CML and how co-morbidities had limited treatment choice or cause imatinib to be stopped:

"I was really struggling because I wasn't sleeping and they couldn't give me anything for the menopause with it being blood related." (PA21)

Some talked about difficulties distinguishing side-effects from symptoms of co-morbidities including pain conditions, diabetes or life course events such as ageing and the menopause. These issues begin to set the experience of CML into the context of a life course, where other events and illnesses are dealt with alongside the blood cancer:

"It's hard to know whether it's because of the medication that I'm on, the painkillers and that sort of thing and I take citalopram which they say can make you feel sleepy, you know, a bit tired. So whether it's to do with leukaemia or whether it's to do with just, well life in general, you know, medication and things like that." (PA06)

Although TKIs may have fewer side-effects than their predecessors, patient data suggests that these are still extremely common and may be prolonged. Symptoms which may appear minor may actually have a significant impact as the chronicity of the disease means they are lived with over a lifetime. The next sub-theme explores how daily life changes as a consequence of CML.

5.1.2 Sub-theme 2: Daily life is changed

Based on the interview data, it can be seen that most patients were living with some effect of the disease and its treatment, despite several having a change in medication or dose. Perhaps then, not surprisingly, almost all expressed how day to day life had been impacted since diagnosis. The most common influence appeared to be on mental well-being, with patients describing a change in mood or general worry, becoming 'upset', 'less positive' and 'losing control', with some accounts of panic attacks and seeking counselling:

"I saw a counsellor about 5 or 6 times because I just really wasn't coping well with it because I felt so sorry for meself, do you know what I mean. I still have off days but all the time I just couldn't cope. I was crying all the time and it's really not like me, yeah really not like me." (PA21)

Accounts revealed a worry about disease progression, which could increase prior to outpatient appointments, alongside greater anxiety over general health issues. This is explored further in *theme 4 (sub-theme 2 perspective on life is changed)*. Another common impact on daily life was employment. With many of the sample of working age, several patients reported they had reduced their hours or stopped working, often due to ill health retirement or redundancy resulting from the disease and its treatment. Specific reasons included fatigue, but also shortness of breath and feeling generally unwell. Some described improvements following such changes, including feeling 'less stressed' and more 'in control' of their time. PA07 had a managerial position involving long hours and a lot of travel:

"So I realised feeling tired all the time, not all the time, but most of the time it wasn't very safe, so I got a chance of taking voluntary redundancy which I did and I'm glad I did now because I've not that level of stress that I had then." (PA07)

Others were more ambivalent, finding it difficult to secure more suitable work, feeling they had no chance of working due to the amount of sick time they would need or not informing their employer about their symptoms due to fear of losing work. PA21, aged 53 at interview, described a particular struggle to secure new employment after retiring on ill health grounds:

“The one thing is I do want to work but I’m limited as to what I think I’m going to be able to do, really limited because of how taking the chemo drugs makes me feel, you know, the fatigue.” (PA21)

PA25, recounted ill health retirement as a difficult time, conveying the message that their employers were not fully understanding of their health changes:

“I had a battle working in the NHS, this was another thing, and it was within my first year, I had a battle with my employer [laugh]. I only worked part-time. I worked 20 hours but that was a struggle because I did it over 4 days. Now with the fatigue I couldn’t, you know.” (PA25)

In contrast, PA30 initially reduced hours, then returned to full time working and also secured promotion, less than two months after diagnosis.

A further impact on daily life expressed was difficulty generally ‘getting around’. A general ‘slowing down’ was described to explain this, along with diarrhoea and the logistics of attending outpatient appointments in those working and living away from home:

“Like I say I was still working at the time as well especially with diarrhoea as you can imagine I were having to pull into like pubs and just run in you know. “It’s not a public toilet”. They don’t understand, you know.” (PA07)

Holidays and travel were complicated by confusion over drug-timing in different time zones, unpredictable energy levels and needing to stay at home for medication delivery.:

“...it’s tricky on the nilotinib is time zones on flights. That’s when it’s really quite tricky because you don’t know whether to start to move your, because if you’re 5 am here you could be anything.” (PA32)

In comparison, PA20 reported that their diagnosis had led them to take a positive decision to plan a long overseas holiday instead of home improvements.

Sporting hobbies were also affected due to fatigue, shortness of breath and diarrhoea, although there was some uncertainty if it could be the effects of age or co-morbidity, again reflecting the context and chronicity of CML:

“I’ve always been very gung-ho about everything, I’ve always walked up mountains and always gone out of my bike and also gone off to the gym or played squash or whatever and I can’t really do that now and it is altering me.” (PA21)

Nilotinib is unlike other TKIs in that it should be taken at least two hours after eating and one hour before eating anything further, twice a day, twelve hours apart. This was specifically mentioned by some patients in relation to the effect on daily routines and meals, with individuals finding it awkward to eat out socially or having to set an alarm to wake up early to take medication. Finally, there were infrequent reports that alcohol tolerance was reduced by the medication, with a single report that this improved after their medication was switched:

“They know that I can’t go but I always get an invite because I can’t eat after 8 o’clock on a night, so I’m just sat watching people” (PA25)

Household jobs such as gardening, pets and shopping were discussed with pain, fatigue, co-morbidity and waiting in for a medication delivery all having a negative impact. In some, sleep was effected by the timing of nilotinib, caring for children was effected by fatigue and appearance changed in terms of thicker hair and feeling the need to undergo a dermal filler procedure. Of note, a small group of patients reported positive lifestyle changes as a result of their diagnosis and treatment including drinking less alcohol, stopping smoking and eating a better diet.

“I stopped smoking straight away before I went, I smoked about 10 after she told me and then threw the packet away and that was it.” (PA20)

On the whole, although most patients reported CML having a negative impact on day to day life, it is worth observing that many also talked positively about the pastimes they still enjoyed, including walking dogs, camper van travel and voluntary work, reminding us of the importance of activity in people’s lives. Indeed, some patients who talked about an impact of CML on their daily life activities, also pointed out that their diagnosis had no impact. Looking closer at the data to understand this apparent contradiction, it appeared that patients were saying that despite CML impacting on certain tasks, in their view they *‘didn’t stop any activities’* and *‘carried on as normal’*.

As with side-effects, the impact of CML on day-to-day life was made more complex by the presence of co-morbidities for some. Co-morbidity commonly effected mobility and *‘getting about’*, also travel and holidays, concentration on reading and sporting activity. Indeed, co-morbidities were sometimes reported to have a greater impact than the CML. These patients were generally dealing with chronic

conditions such as renal failure, diabetes and arthritis. PA26, diagnosed around eight years previously, described how the effect of CML changed as her co-morbidity developed:

“My stroke limits me more than my leukaemia. I can cope with that easily” (PA26)

Finally, patients were also frequently affected by significant social and financial issues unrelated to their CML and its treatment. This included loss of benefits, redundancy, marital breakdown and the death of a loved one. Again, patient accounts of the influence of co-morbidity and social issues on daily life reminds us of the social context of CML:

“So they said that he wasn’t poorly enough to need a mobility car. He was fit and healthy. He could drive quite well because it was adapted to his needs.” (Relative)

5.1.3 Summary of theme 1

Although relatively speaking, the side-effects reported by patients and effects on daily life may not seem as devastating as in more acute diseases, when set in the context of chronicity and the life long course of CML such effects may be experienced on a daily basis and therefore significantly influence quality of life. Impacts on daily life such as employment, sport and meals have the potential to undermine confidence and restrict social activities. The following theme explores how the impact of CML may be mitigated by the external influence of social support.

5.2 Theme 2: Social support level and type matters

The benefit of social support was discussed by all patients in the study. Family, friends and/or others helped not only by acting as advocates, but also by sharing the emotion of living with CML, and by providing practical help with day-to-day tasks. When talking about family and friends, patients used words such as ‘support’, ‘close’, ‘looking after’, ‘coping’ and ‘keeping in touch’, describing the ‘softer’ aspect of a caring role.

“Yeah they’re always making sure that I’m alright which is nice.” (PA15)

Patients also mentioned supportive employers, who offered measures such as working from home, flexible hours and time off for appointments. Some spoke of the support they experienced from MacMillan Cancer Centres, and others discussed support from online communities and their religious faith:

"I'm quite happy going [to haematology clinic] every 3 months. It reassures me that everything is going on, so although it does mean that I come out of work pretty much an afternoon every 3 months, my work is supportive, I can do that." (PA30)

The way in which social support networks shared in patient emotions was often recounted and was particularly apparent at diagnosis, when parents, spouses and children were shocked and upset:

"So eventually a nurse and a doctor came in and they sat down and they were quite straightforward and he sat right in front of me, full eye contact, 'we [are] querying chronic myeloid leukaemia'. Well my husband fell back and I just sat there." (PA25)

Some patients explained that over time, family members tended to worry less about them, however some became more emotionally labile and anxious. Relatives were sometimes described as perceptive, knowing when the patient was unwell or upset and accompanying them to appointments because of this:

"My other half, I mean she knows when I'm tired. I mean I came in last night and I'd had an absolutely busy day at work yesterday and she just went...you don't need to do anything...just go sit down and she could tell I was absolutely zonked." (PA24)

Several patients referred to their family and friends acting as advocates on their behalf. This often involved listening to information at appointments, communicating with the doctor or nurse when there were health concerns and reminding the patient to take their medication:

"I'm glad that I took me wife there with me because she was sort of, not translating, but she was taking more in than I was, you know." (PA07)

Many patients described how family and friends helped with practical tasks such as shopping, collecting prescriptions, personal care, and also with transport to the hospital clinic. Companionship from family and friends was discussed and considered important by some:

"...my auntie lives just opposite in the high rise flats and we go to bingo on a Friday night, so sometimes I'll say oh will you go and get my tablets and she'll bring them down for me." (PA06)

Patients also spoke about the effects of stressful events in family life including the loss of a loved one, underscoring the benefit of support from family and friends at such times. This again emphasises the chronicity of CML and how it becomes part of life alongside other experiences, including bereavement, family illness and relationship breakdown:

"I lost my husband in 2006, I'm sure the grief and the stress of that watching him die, it was horrible. I mean it was just horrible. I could still just burst into tears, you know, still after all these years and I'm sure that affects you physically, you know." (PA04)

Despite speaking positively about their social networks, several patients discussed times when such support was lacking or difficult to access, also times when their own caring and supportive role towards others in their social network could be limited, highlighting the complexity of relationships. There were occasions where other people could not be relied on, were unhelpful, or who the patient felt they could not approach, so as to protect them from worry:

"...my daughter is not the worst one but I don't think she likes to think of a mum as being ill and she's a keep-fit fanatic and can you just do this and I aren't really feeling up to that today and then she'll realise and then maybe kick herself for asking but I don't like refusing, you know." (PA25)

There were accounts from patients describing a different cancer diagnosis in someone they knew. Other's experience of cancer could cause patients more or less worry. Some patients concluded from their experience of other's cancer that the disease 'effects everyone' and they 'felt lucky' in comparison:

"I do sometimes sit and worry about it and I think because my mum, like I said, had ovarian cancer but she was diagnosed just before her 60th birthday and then it affected her in a really bad way mentally as well as physically but she died when she was 62 and I've always had it in my head that that's when I'll die and I'm 58 now, 59 this year." (PA06)

In a wider sense, patients also discussed the reaction of people around them to their diagnosis. There was concern and shock from some, which seemed to diminish as others realised the patient wasn't acutely unwell and didn't 'look ill'. This 'disease journey' is explored from the patient's point of view in *theme 4 (sub-theme 2 perspective on life is changed)*.

5.2.1 Summary of theme 2

This theme demonstrated that social networks offered support, with family and friends providing the softer aspects of care, including protection from the emotional impact of CML, as well as practical help. They also had an important role in advocacy, helping the patient understand information and liaise with medical staff, influencing their disease knowledge and awareness. However, this support is not always consistent and some are unwilling or unable to provide it. Patients themselves may also have caring responsibilities. This lack of support could negatively influence disease impact as well as create a more negative life perspective. Life events, such as bereavement and relationship breakdown, also impacted on the CML experience, highlighting the life-long course of the disease. Patients often use the experiences of cancer diagnosis among other people in their network as a reference point for their own pathway, causing more or less worry and affecting their perspective on life with CML. The next theme describes a second external influence on the patient experience, hospital care.

5.3 Theme 3: Hospital care: good and bad

All patients were cared for by a hospital haematology team, mostly in outpatient clinic with a doctor or consultant, and three interviewees were managed via nurse-led telephone clinic. When discussing this, patients tended to describe the process as a predictable routine occurring every three months, involving a blood test, often being weighed, and then waiting to see a doctor. The nurse led clinic differed in that patients had their blood taken locally, or at the hospital, followed by a phone call from the CNS. When they saw their practitioner, patients reported that they had their blood results explained, often received a prescription and were asked how they were feeling. Contradictory views about the merits and drawbacks of the hospital system were expressed, as explained below.

The nature of staff

Many patients referred to the positive nature of hospital staff, commonly using words including *'helpful'*, *'good'* and *'nice'*, and in even more favourable terms by some; *'wonderful'*, *'beautiful'*, *'brilliant'*. When this was put into context, patients described how all types of staff were on first name terms with them, that they offered them their help, and how doctors talked honestly. PA11, an elderly male patient with several co-morbidities, explained why he felt so positive about the hospital staff:

“I’m really, really happy with haematology and that. I mean you couldn’t ask for a better team. I mean even [down] to receptionists, there must be hundreds of people go through haematology for different things. She knows everybody by their first name.”
(PA11)

Notably, PA30 reported a health care professional having an unpleasant manner:

“I saw a guy last year and he was obviously, he’d been away for a while and come back, he was one of the registrars or whatever, I didn’t particularly like him. I did mention to the nurse that perhaps he needs to work on his bedside manner a little bit.” (PA30)

Interestingly, the same proportion of patients who discussed positive aspects of hospital care also reported negative aspects, and these seemed to be more specific. Furthermore, there was no evidence of overall opinions of poor hospital care, in contrast to several examples of patients reporting a positive experience in general. These mixed opinions are described concurrently in the remainder of this theme.

Communication

Many patients described how their practitioner offered them helpful explanations regarding disease and treatment. More specifically, patients often described the reassurance this offered, which was particularly evident during discussions about prognosis:

“Yeah but I think once they’d explained everything to me and it was very positive, you know, and when he said if we’d been talking to you how many years ago, it would have been a different scenario. That sort of sunk in.” (PA20)

PA15 and PA21 both referred to the way the disease and treatment were explained as a positive experience:

“Oh they’re just brilliant. They just make you feel at ease, you know, they explain stuff to you, just nice people, really nice.” (PA15)

However, PA21, a recently diagnosed middle-aged woman, later recounted how her consultant didn’t discuss prognosis in the depth she wanted, to satisfy her concerns:

"...so I did have a quick look on the internet about life expectancy and so on because Dr [consultant name] he didn't want to talk about it." (PA21)

Despite patients reports of helpful explanations from hospital staff, aspects of poor communication were also described. Some felt staff didn't or couldn't listen to their concerns about side-effects or symptoms. PA28 and PA29 both had multiple co-morbidities and talked about how they felt certain problems, which may or may not have been related to their disease and treatment, were unheard:

"I've to be careful what I tell her because if I tell her [CNS] owt about the toilet, "I don't want to know anything about that" because my toilet, you know when I go, it's either diarrhoea, it's either constipation." (PA28)

PA25, described being spoken to in an 'assertive' manner by a consultant when advising her to take a new drug that she was hesitant about, but which she later felt was the right decision, as the treatment was successful with less side-effects than expected. However, the impact of this approach was reflected when discussing how she would deal with new symptoms or side-effects:

"If it's nothing – if I'm not really concerned about it, I'll just see how it goes. I don't usually report anything because I think after getting my knuckles rapped by Dr [consultant's name] that time, I think do they really want to know? [laugh] So I don't really report anything." (PA25)

PA24 was mentioned earlier in *theme 1 (sub-theme 1 symptoms, side-effects and varying treatment success)* due to significant fatigue, which he felt was not dealt with well via the phone clinic:

"Yeah I get the phone call and I do say stuff over the phone but I often think it just falls on deaf ears and just think, yeah that's par for the course really and that's it." (PA24)

PA24 also said this fatigue had caused him to reduce his TKI dose, based on advice from an alternative therapist. He went on to say that if he experiences symptoms now, such as fatigue: *"I just keep it to myself to be fair."* PA27 and his relative, monitored by the nurse led phone clinic, spoke about how only their GP dealt with medication side-effects:

PA27: "I mean he [the GP] just looks at me notes and obviously he just tells me to go and see me specialist really, that's all he can do."

Relative: "Because the specialist only wants to see him if he's got concerns about your leukaemia doesn't he but anything else that's a side-effect from the medication like gout and all that, the doctor has to deal with."

However, some patients also reported side-effects being dealt with effectively and efficiently:

"...when we switched to Bosutinib they were straight on it with the Imodium, whatever that's called, and some anti-nausea stuff. So for the stuff that they knew was going to hit you, they were very proactive on that." (PA32)

PA30 was impressed with the specialist opinion sought at a time when she was experiencing significant side-effects to her TKI:

"...when they were deciding what to do with me whether to put me back onto Glivec or what they were going to do to it, they had a case conference with the team in [hospital with cancer centre], the lead consultant in [hospital with cancer centre], there was a case conference and I was put forward as a case to be discussed and decided upon and they've come up with a plan." (PA30)

Several patients also referred to explanations about disease response, procedures and written information in a positive light. PA07 talked about how his response was explained in clinic:

"They're quite informative down there when you go, you know, they show you the screen and say well that's where you were and that's how you're reacting to this and as long as it's on a downward spiral or keeping in the green, I'm happy with that and I think they are down there, you know." (PA07)

However, PA07 also recounted how he couldn't understand the doctor who spoke in a different accent to himself and felt overwhelmed with information at diagnosis:

“They just give me a book from Macmillan to look through which, and I was just reading through it and there was a bit too much information in that really, you know, and I didn’t really take on-board how serious it was to tell you the truth.” (PA07)

In contrast, two others (PA11 and PA21) felt the written information at diagnosis provided a useful explanation of their disease:

“I did read through all the bumf and I did get the gist of everything. It was good. It explained really well in lay-man’s terms, not so that I couldn’t understand it which was really good.” (PA11).

A small number of patients expressed their appreciation for having a relative present at their appointments and an apparent awareness among hospital staff that they also needed the disease and treatment explained to them:

“But they were very good at explaining things because I’d gone on my own that day when I got the results. Well they made me another appointment and my son and daughter came with me and they explained more about what’s going on and, you know.” (PA06)

PA24 however gives a differing account, not having been advised to bring a relative or friend when he received his diagnosis:

“They didn’t actually say to me come through with somebody, I just went through by myself. So there I was sort of like reeling with the fact that I’d been told I had leukaemia and had all these tests on me in the afternoon and then I had to sort of get me self-home.” (PA24)

There were a few concerns about the cause of CML, something these patients hadn’t discussed with clinical staff, implying their appointments were focussed on their CML management, rather than talking about the cause:

“No I’ve never actually discussed it. I just discuss more or less what’s going on now.” (PA19)

PA26, an elderly lady with several co-morbidities, also avoided raising concerns about prognosis in her appointments, despite feelings of anxiety about this:

PA26: "The thing that worries me, as I said, was the older I get the more I think that my luck is going to end soon. I don't know. I don't know if it will."

AH: "And would that be something that you chat about with [CNS name]?"

PA26: "No. I've kept it to myself until now."

Psychosocial support

Several patients talked about positive aspects of their relationship with their practitioner, which made them feel worthwhile and secure. They referred to the ability to talk about their feelings and concerns with doctors and/or nurses:

"...if you have any worries you can get in touch and she [the CNS] puts it right which she's very good. You can't ask for anything else." (PA11)

Some patients talked about a closeness with their health care team and their ability to reassure them. PA06 discussed a member of the clinical trials team who conducted her bone marrow test after returning from maternity leave:

"...she'd just come back to work and yet she come and said, oh [PA06 name] I'm so pleased to see you and she gave me a right big hug and, you know, it's that closeness even though they're not people I know that well but it's nice, you know, there's that closeness." (PA06)

Other patients referred to the level of trust in their health care professionals. PA29 recounted a conversation with her consultant about entering a clinical trial and his advice against it:

"...he said I know it'll bring you out for a stem cell transplant and you don't need it at this [point] and pray he said, it never will do and I believed him, every word, word for word, I believed him." (PA29)

This was followed by a period of anxiety, as her consultant needed to secure funding for the new imatinib, but PA29 was eventually prescribed this drug and continued on it. PA32 referred to building a relationship with his consultant during the diagnosis stage, when treatment pathways

were explained to him. Here he explains the importance that his relationship has in coping with this treatment:

"...you invest your time in it and you know it will do you good and, you know, it's good to have at least some form of relationship with the consultant because he's quite good to get on with." (PA32)

Some patients, however, expressed feelings of being a nuisance to clinical staff, or a fraud. PA15 talked about how his wife supported him with this:

"...well at first she was a bit, well more supportive I think because I used to come back and say, I feel out of place really because there's a load of poorly people and, you know, so...but no we go together." (PA15)

PA29, diagnosed several years ago and living with other co-morbidities reported how she felt a 'nuisance' to the hospital team:

"...she's [CNS] always busy and that, and you sort of feel, you get to the point and I got to the point when you think I've had it that long they really don't want to know." (PA29)

Clinical expertise

Patients also spoke about how effective health care professionals were in terms of their clinical expertise. This covered managing treatment and co-morbidities. PA28 described here his treatment for a pericardial effusion, which was related to his TKI:

"I won't say I'd call it surgery, but he came up and they brought, I think there were 46 round bed watching because this was a new technique entirely where they stick a needle in between your ribs and it goes into the pericardial sac." (PA28)

Although there were few negative comments on aspects of clinical care, the most frequent related to the bone marrow sampling procedure. Whilst a few described this positively, this was often reported as a negative experience. Depicting a good experience, PA15 said:

"...he said it might hurt but it's not hurt me at all, and they let the wife sit in on the last one because I just thought it was a needle going in but it isn't and I was absolutely amazed. My wife thought that was brilliant." (PA15)

Several more, however, described the test wholly negatively with words such as 'terrible', 'horrible' and 'intrusive':

"It's like being stabbed in the back, it really is." (PA27)

Health System

Patients frequently commented about the efficiency of their hospital care, often relating to the speed of referral and diagnosis but also the functioning of clinics and delivery of medication. However, others, or sometimes the same people, also spoke of areas where they felt their hospital care was inefficient, usually in terms of missed or delayed tests/results/letters, waiting times in clinic and prescription problems.

Some talked about the speed of GP referral to first hospital appointment, which ranged from "straight away" (PA02) to two days. The time from GP referral to diagnosis was described; some reporting waiting 1 day from first seeing their GP to being seen in hospital,. In contrast PA21 described waiting around a month from GP blood test to hospital diagnosis, which PA21 actually described as 'quick'. Other patients felt the period between diagnosis and start of treatment was efficient, PA20 reporting it to be 7 hours and PA19 within a day. PA02 reported around a month's wait between diagnosis and treatment start.

Aspects of the outpatient system which were felt to be positive were also discussed, including clinics running smoothly, access to CNSs, short waiting times, and prompt blood results. PA15 described the outpatient clinic at his hospital, saying:

"Everything seemed to just run smooth. They don't rush you, it's just relaxed." (PA15)

PA32 mentioned how he appreciated being able to contact his CNS via text:

"I tend to text her because she responds to text, you know, she's clearly a busy person. I mean I find email and texting quite handy because it's an easy way of contacting." (PA32)

PA07 praised the hospital for being flexible to fit in with his holidays:

“No and I’ve worked round, sort of cause I’m on holiday a lot now and they’ve sort of worked around my holidays, so that’s good as well like. I can stock up on medication as well.” (PA07)

Despite many reports of efficient referrals and positive aspects of outpatient care, there were also negative comments. Several patients talked about long waits in outpatient clinics, usually between having blood taken and seeing the doctor, but also excessive waits for prescriptions and to see the doctor as an inpatient, alongside uncomfortable seating and high parking costs. Patients transferred to the nurse led phone clinic said this was an improvement on long clinic waits, PA26 recalling his previous appointments in the hospital:

“I think so yeah because you know, you’re sitting there for maybe an hour and a half and it’s boring. It’s nice when you go in to see the doctor but I’m fed up by then, yeah.” (PA26)

There were accounts of problems with missed or delayed tests, results or outpatient follow up letters. PA07, for example, points out how late appointments may mean he misses his test results:

“Sometimes the only trouble with that is when I get a later appointment, I get a late appointment round about 4.30 and they take me bloods and then we don’t get the results then because the haematologists have gone home.” (PA07)

Several patients reported problems with their prescriptions, including either running out before their next appointment, or pharmacy not stocking enough of the right medication, or right dose of medication. For some patients this occurred infrequently:

“A few times I’ve had it where I’ve run out of tablets before my appointment was due.” (PA06)

PA06 reported hospital staff quickly arranging a new prescription after she contacted them, and improvements in the situation:

“But it’s only happened a couple of times has that and now it seems to be, you know, because he (consultant) put a note on the files that it must not happen.” (PA06)

Others however, described a seemingly regular issue with hospital pharmacy stocks not having enough, or the right dose of their medication. This could result in patients needing to return to the hospital to collect extra medication, which as PA30 pointed out, requires them to remember to do this:

"I end up having to go back and get them which is not too bad because I work in [local city] and I can, because of the hours that I work, I can time it and go and collect them on the way in to work. I've just got to remember to go and do it." (PA30)

PA32 described arranging his own extra TKIs, with support from his consultant, to mitigate against the pharmacy not routinely stocking his medication, and to avoid having to miss doses:

"What I said to him [consultant] I said well can you prescribe me a buffer? So I've now got about a week's worth of buffer. What sometimes I like is when they forget how much they've ordered for me and they'll order a bit, so they'll give me 3 months." (PA32)

Some patients received home delivery of their medication, or delivery to a local chemist, which they generally found more convenient:

"Yeah it's better than driving all the way and not being able to get parked at the hospital, you know, it's just like going shopping up there and they're always there in time for me." (PA25)

PA04 however, was not initially happy with home delivery, feeling this was restrictive, particularly to her holidays, as she previously collected three months medication from the local hospital at a time of her choosing. As a result, she negotiated an increase from monthly to bi-monthly home delivery of her prescriptions:

"I've got to be here to receive them and so that's very tying for me in the summer months when I want to be off in my van because I've got to be back on Tuesday for my tablets." (PA04)

There were comments about continuity of care, and whether patients saw the same doctor at each appointment. Some patients, who saw the same consultant, felt this allowed them to get to know their doctor better:

"I started seeing Dr [consultant name] on a regular sort of basis and you get to know him a bit better and I've been seeing him sort of regular." (PA07)

However, patients also described the drawbacks of seeing a doctor they didn't know, and PA02 described seeing a 'stand in doctor' who didn't prescribe enough tablets.

"You almost certainly don't know who I am. I know it's not a personal service, I accept that, I don't have a problem with that but I'm thinking you're just winging it, not winging it, but you've got no real knowledge of my case." (PA32)

Several patients discussed hospital parking. This was reported to be so busy that patients had to find alternative parking, wait a long time for a space, or get dropped off, meaning the patient attended their appointment alone:

"He drops me at out-patients west, where I go and sit in and my daughter lives down the road so he goes there. But then, you know, like I say, when I have an emotional day, you know, I think well sometimes other people are there with partners and husbands and I feel on my own." (PA29)

Patients also reported expensive parking charges and difficulty anticipating the required length of stay. Finally, patients raised issues about IT access as part of their hospital care. PA07, for example, was unable to use his electronic device at his initial inpatient stay, so could not search for information about his disease. PA32 would like the option of emailing the hospital to rearrange appointments:

"I think from a CML perspective having [CNS name] there to contact is great but is just a few general things, you know, you'd just like to fire an email of. So more, that routine stuff it would be nice to have a mechanism for interacting with that. It would be nice to reschedule appointments on-line but it's relatively minor stuff." (PA32)

Primary Care

Some patients spoke positively about GP care, notably about service efficiency and their relationship with their GP. Patients spoke about the rapidity with which their GP investigated their symptoms and referred them to hospital, and also how easy it was to get a GP appointment:

“The GP they are good, they’re pretty good and you can get in the same day if you ring up which is great.” (PA21)

Some said they felt they could talk to their GP, who was reliable and understanding, listened and took special care of them due to their CML and PA19 was disappointed his regular GP was retiring:

“It is a shame when you’ve had a long standing, like they become a casual friend sort of thing, do you know what I mean.” (PA19)

However, PA29 and PA30, as discussed in *theme 1 (sub-theme 1: symptoms, side-effects and varying treatment success)* had negative experiences at the time of diagnosis with perceptions of delayed hospital referral. In further comments, PA11 described being advised to call haematology about symptoms as his GP wouldn’t have the required specialist knowledge of CML, and PA20 described how her haematologist was angry that her GP surgery shut during the day, preventing him from arranging her admission at diagnosis.

“But he did just say that he’d got the results and he rang the surgery at [local town] to get in touch with me and he was astounded because the surgery shuts for an hour and he had a bed.” (PA20)

5.3.1 Summary of theme 3

The patient group spoke about positive and negative aspects of hospital care, and most had ambivalent reports. Whilst this may demonstrate varied individual opinions, it may also reflect differences in care delivery across hospitals and staff. However, although opinions were mixed, negative comments appeared specific, with many patients referring to their overall care in a positive light.

Several positive comments referred to the softer aspects of the hospital practitioners’ role referring to the nature of staff, and around half the patients described positive aspects of their psychosocial care. Some of these reports also referred to GPs. This highlights the value patients placed on aspects of care such as an ability to talk to, and access, their doctor/nurse and feeling reassured, which may support them in their disease management. Patients also appreciated the clear explanations they received, particularly around prognosis, disease, treatment and response. Such knowledge and information again may support their ability to self-manage. This contrasts with reports of less adequate explanations around side-effects and symptoms in follow up appointments. Several

patients felt reluctant to talk about their symptoms or side-effects, or felt the doctors and nurses were reluctant to do so. This is concerning due to the clear impact of side-effects on daily life, described in *theme 1*. Finally, patients praised the clinical expertise of their practitioner. However, many described their bone marrow sampling procedure in particularly negative terms, adding to the already significant impact of their disease and treatment.

There were mixed reports regarding hospital systems of diagnosis and ongoing outpatient care. Often, patients praised the efficiency of their hospital, commonly in relation to rapid appointments around the time of diagnosis, with several patients also describing the outpatient system as running smoothly with prompt test results. However, there were also reports of missed or delayed results or outpatient follow up letters, long waiting times in outpatients' and some described running out of medication too early or inadequate pharmacy stock. In some areas these problems were avoided through the use of a pharmacy home delivery service and nurse led telephone clinics, however these services were in the minority and not all patients saw them as a positive. Finally, difficulties with hospital parking were a concern for several patients, in addition to a lack of continuity of care and poor access to IT. Such systematic problems are outside of the control of patients and sometimes practitioners, but could clearly impact on disease management.

5.4 Theme 4: Personal influence

Theme four describes how patients make sense of their disease in terms of both their knowledge and perspectives. These are referred to as personal influences on management of the disease as they are not external influences, such as social support and hospital care.

5.4.1 Sub-theme 1: Disease knowledge and awareness varies

Most patients conveyed their level of disease understanding throughout their interview which is described within this sub-theme. The main areas discussed were awareness of disease response, disease pathway and treatment. The level of knowledge and awareness in these areas differed between and within individuals. Also, within this sub-theme is the idea that some patients preferred to receive less information, and perspectives on the format of the material shared with them.

Disease response

Of all the areas mentioned above, patients seemed to show greatest knowledge about how their disease was monitored. Patients described their molecular response and understood this in terms of the graph of BCR-ABL levels over time, routinely provided by HMDS. They referred to this as '*the graph*', '*being in the green*', '*rising*' or '*coming down*' and where the '*stars*' were:

"...the last time I went, we're on November now, in August I'd just got into the green so that's what they were aiming for." (PA07)

Several also referred more specifically to medical terminology when describing their molecular response using the terms 'BCR-ABL level', 'MMR' and 'log reduction':

"I know I've been under the line but I've never, ever, ever had a 0.000, never. I've been 0.001 and 0.002, up to 4, and I came off it and I was off it for 8 weeks and they tested me and it started rising, the PCR was rising." (PA29)

Patients discussed blood counts as a way of disease monitoring, mentioning their full blood count, white cell count and liver function and bone marrow samples used to measure response in the early stages of disease:

"I understand where my white blood count has to be, something in between 4 or 10 or something like that." (PA30)

A minority of patients were not clear on how their disease response was monitored:

AH: "...do you remember anything they might have told you about your response, so how they're measuring how well the tablets are working?"

PA11: "Not a right lot no. They measure summat to do with the blood."

Disease treatment

The second aspect of knowledge and awareness was treatment, with patients showing greater and lesser levels of understanding in almost equal measure, with varying levels of knowledge commonly found in the same individual on different aspects of their treatment. Many patients reported features of what TKI drugs do in the body, and there seemed to be little misunderstanding of this. Some patients reported a basic understanding of how TKI drugs worked to control the disease, others discussed more specific aspects including enzyme blocking, controlling the white cell count and keeping the level of a chromosome down:

“The enzyme attaches to the white blood cell which causes the white blood cell not to mature, so you build and build and build and it’s like a block that stops that. So I understand that process and how that works.” (PA30)

There seemed to be little misunderstanding of drug regime. Some recounted the timing of their medication, one recalling advice to take imatinib before bed and with food, and three of these four who were on nilotinib, reported a more complicated regime:

“Tablets at 5, straight back to sleep, then by the time I’d actually got up at 7 or 8 o’clock that’s fine I could eat and it’s a bit more friendly in the afternoons. So 3, 5 eating at 6 so that worked fine but you’ve got to establish that pattern.” (PA32)

However, there were aspects of treatment where some patients were less aware, one of these being side-effects. Some patients were unsure about whether their symptoms were treatment related, or reported having received minimal information about treatment effects:

“Never had the energy and to be fair, I’ve never really spoke to anybody else who has the same symptoms or on the same medication to find out what other effects people have. So I wouldn’t know whether it’s part of it or what really.” (PA24)

PA07, diagnosed relatively recently, reported he would like to know more about a possible cure and one patient who was diagnosed and started on TKIs pre-2004, reported not knowing about their medication, implying they had been told but had forgotten:

“They gave me information on, you know, what happens next and, you know, what treatment I should be having but it was that long ago now isn’t it yeah.” (PA27)

PA20, a newly diagnosed patient, mistakenly believed she was taking chemotherapy and asked me to explain what targeted therapy was:

AH “Chemotherapy was tried but it wasn’t, it comes with a lot of side-effects, it wasn’t as successful as these drugs.”

PA20 “So what are these then?”

Finally PA21, who could recall details of her dosage being reduced due to side-effects, believed she only required a half dose, suggesting she had been informed her disease was responding adequately.

From examining HMDS BCR-ABL levels, this patient had failed to hit ELN guidance treatment milestones which I later discussed with the lead clinician for CML:

“I think the last bloods they sent to Leeds was something like down to 4% or just under 4% which is amazing, you know, from where it came from...I think most people end up being on the full dose whereas I’ve done really well so I only need half the dose which is good for me.” (PA21)

Some patients recounted being told about the availability of other TKIs if needed, and found this reassuring. PA04, however, reported she wasn’t aware other drugs were available:

AH “...what they call second generation drugs for chronic myeloid leukaemia, is that something that ever comes up?”

PA04 “No it never has, I just seem to carry on with whatever because it’s doing okay.”

PA20 and PA24 discussed their understanding about stopping TKIs, explaining, appropriately, that this would have to be carried out in a “*controlled environment*” (PA24). Results from large scale ‘stopping’ trials weren’t available at the time of the interviews:

“...nobody has come off them to see yet or the trials aren’t back, to see whether it’s the drugs that have killed it or cured it or still keeping it at bay. I think he said it was going to be another 18 months before they knew.” (PA20)

In contrast, there were accounts of patients seeming fully unaware that this was potentially something that would occur in the UK. Patients also discussed the cost of TKI drugs to the NHS, conveying awareness of how their drug was more expensive than others, that building up a stock of medication at home would come at extra cost to the NHS, and that NICE assessments considered cost effectiveness:

“I mean obviously it’s a really expensive drug so I tend to make sure that I’ve not got a load in stock sort of thing.” (PA07)

Interestingly there seemed little explicit discussion about how important patients felt it was to take their medication regularly other than their understanding, discussed earlier, about how TKI medication worked in the body. It is possible that there was an implicit understanding that taking

their drugs as prescribed was important to their disease response and this is examined in more depth in *theme 5 (managing the disease is individual)*.

Disease pathway

Patients showed a level of knowledge and awareness of the disease process and pathway, with some having less understanding, and with similar variations of understanding within individual patients. Several patients reported an understanding that CML was a chronic rather than an aggressive cancer and around a third expressed some understanding of the disease process in CML, including genetic mutation, the involvement of stem cells, the Philadelphia chromosome and abnormal blood counts:

“There’s a little jumping, you know, a gene and it jumps and crosses over somewhere where it shouldn’t and basically that’s what causes the problem I believe.” (PA04)

However, PA28 mistook the Philadelphia chromosome for the “*Pennsylvanian strain*”, believing he could have passed this down to his children:

“They say Pennsylvania strain what I’ve got, which I don’t know what that is, I don’t know. I suppose it’s one type of leukaemia...if I’ve got this faulty gene, will it be passed down in any way?” (PA28)

There were accounts of an understanding that CML differed from more aggressive, acute leukaemia, and others conveyed their knowledge of CML prognosis:

“...to be relatively grateful if it did prove to be CML to be living in the 21st century rather than the 20th century because the outcomes are chalk and cheese aren’t they.”(PA32)

Of concern, PA02 and PA21 seemed to have misunderstood their prognosis and outlook. Mentioned earlier, PA21 seemed to believe her BCR-ABL response implied a good outlook, although she was not reaching ELN treatment milestones and PA02, diagnosed in 2009, implied he was given five years to live, perhaps misunderstanding a conversation about five year survival:

“...they found it was leukaemia. And I was told I had at least five years to (inaudible) this was about 8 years ago.” (PA02)

An area of interest to several patients was the cause of their CML. Some patients discussed their knowledge of possible causes, such as radiation and benzene, gained either through information they were provided with or from looking on the internet. There was concern from others who

questioned if previous radiotherapy or infections may be a link and PA24 expressed a concern about previous employment:

"I mean one of the first things, questions they asked me was did I work in a petrochemical industry. I mean I think Benzene." (PA24)

A small group of patients eluded to the idea they had less need for information and knowledge about their disease and response. They preferred to simply know that things were going well without further detail, or they avoided researching disease information:

"No I didn't delve into it. I was quite happy to take my tablet every day and leave it then to my 3 monthly check-up, you know." (PA04)

Information format

In *theme 3 (hospital care: good and bad)* the importance of effective verbal explanations from practitioners was clear, particularly around prognosis but also the disease pathway and treatment. Several patients also discussed non-verbal information they received or found, either from written information or the internet. Patients were generally positive about the leaflets and booklets they were given; the written information clearly explaining the disease, and this understanding, about possible causes, prognosis and side-effects, could be reassuring. There were accounts of being given too much written material initially, however also that over time this proved useful and was also valuable for family and friends to read:

"I'd just show them the booklet, you read up on that and they'll say, oh I didn't know that, didn't know this, the booklets are really useful." (PA15)

Despite finding written information made things clearer, PA07 felt that the section on end of life was too daunting to read:

"It's like that Macmillan book. There were like passages in there saying how to tell your children, you know, if you think you're going to die and stuff and you're thinking, god I don't want to be having this discussion with them, you know." (PA07)

A number of the group also spoke about information on the internet. These patients didn't mention whether or not they were guided to websites by their doctor or nurse. Some seemed to have been

advised, or held a belief, that it was best not to look on the internet, PA25 reporting this could be frightening:

“Some things I read can still frighten me but I think even, you know.” (PA25)

Topics patients researched on the internet, either at diagnosis or as they began to live with the disease, included the causes of CML, changes to treatment, side-effects, prognosis and the disease in general. PA32 explained how a combination of information including his own internet research made things clear to him at diagnosis:

“So partly combination of the doctors and nurses and part of it through going off and finding materials and getting my head round it. I knew roughly what the treatment pathway looked like from that weekend.” (PA32)

PA07 and PA24 talked about the CML online forum, one using it to investigate information about stopping TKI drugs (PA24) and PA07 finding it a more negative experience:

“There’s a CML forum isn’t there and I started reading that but a lot of people seemed to be depressed on it and I thought I don’t want to read anymore. They’re all sort of despondent, you know”. (PA07)

5.4.2 Sub-theme 2: Perspective on life is changed

This sub-theme was discussed by most patients in terms of the initial psychological impact of CML, how they made sense of the disease and see it currently, and their hopes and worries for the future. It was evident that for most, their perspective on life had been changed by their diagnosis.

Shock at diagnosis

Almost all the group spoke about the shock they felt when told they had CML, often recalling this clearly and being able to describe it within the context of what they were doing at that point:

“So I then came back to take the dog out and as I had the dog in the car going down to the park I got a phone call on my hands-free set in the car from my GP telling me, he just told me I had cancer.” (PA07)

Several patients described how the diagnosis was unexpected, difficult to believe and upsetting: PA30, described earlier in *theme1 (significant impact of disease)*, recalled her diagnosis being initiated at the opticians:

“She came back in and said, look you’ve been haemorrhaging at the back of your eyes. I sat out in the opticians crying my eyes out thinking what the hell is going on.” (PA30)

Some also talked about how the speed of the diagnostic process had compounded the feeling of shock. PA25 described being at work and missing calls from her GP about her blood test results, and her husband then receiving a hand delivered letter from the surgery receptionist:

“He’d got home, he’d found the letter through the door from the doctor’s receptionist saying could I ring the practice immediately or could I ring the...hospital, there was a doctor waiting to see me and I needed to be admitted and I was, what the hell is going on?” (PA25)

Interestingly, in *theme 1 (significant impact of disease)* it was noted that most patients reported symptoms pre-diagnosis, which were commonly non-specific, or they said they generally felt well, which perhaps also contributed to the shock:

“It was a funny feeling really, it was just like a bit of numbness at first because I’ve never been poorly. I never go to the doctors. So it was like a bit of a bombshell. It probably took 2 week for it really to sink in for me but it upset the wife straightaway.” (PA15)

Many also talked about the fear their diagnosis created, stemming from hearing the terms ‘cancer’ and ‘leukaemia’ and ultimately a fear of death:

“I suppose when I was told I had leukaemia, I mean there’s so many different kinds of leukaemia that, you know, just the word leukaemia it strikes fear into your heart.” (PA04)

Positive perspectives on life

Typically, patients suggested they had accepted their diagnosis, had begun to continue with normal daily life, or even forgot about their disease. Rather than merely the passing of time, this acceptance seemed to result from learning more about the disease and its chronicity, seeing the TKIs successfully control their CML, or overriding concerns about co-morbidities. This is reflected in the

thematic synthesis which found the process of adaptation to be active, not just due to the passing of time. PA15 described her change from upset and shocked to a more positive perspective:

“I got introduced to the nurses and they gave me some information and I started reading up on it and I’m thinking, oh it’s not as bad as what – it’s probably one of the best cancers to get if you’re going to get it. So I was positive then and thinking right I can cope with this.” (PA15)

PA30, who suggested that acceptance was a conscious decision made by the patient, rather than a passive phenomenon, spoke about a choice between ignoring and accepting the disease:

“You can either curl up in the corner and not get on with it or you have to accept that’s what it is, work with the people that are helping you and hopefully you are well enough and able enough to take that forward. I did have dark days really but, you know, you just get on with it really.” (PA30)

Common to several patients was an awareness that, having considered the possibility of death, they were still alive. Some referred to feeling lucky and described how they now appreciated life, prioritising people and activities that were important to them. Some also expressed gratitude about the availability of TKIs, and the research preceding this:

“I’ve been lucky, I’ve lived for so long and I’ve got a lovely family and I’ve seen my grandchildren. You come to terms with these things. You have no option actually, you know, you do think about things and you hear the news and what’s happening to others, you know, and you think well what are you to complain about?” (PA04)

“But we just live for us holidays now, and it’s made me appreciate life a lot more, you know.” (PA07)

“Without that medicine in the 21st century, I’d be pushing daisies up, you know, I’d be dead by now.” (PA32)

Despite the negative impact of the disease and its side-effects, there were also accounts of positive lifestyle changes as a result of their diagnosis, as discussed in *theme 1 (significant impact of disease)*:

I've been thinking I want a new kitchen in there and I'm thinking, do you know, kitchens, they don't make your memories do they? And, you know, if I went back to the hospital, god forbid, hopefully not this time, I don't know 6 months' time and they suddenly say, it's changed...they wouldn't let me fly and then you can't do it [travel] again, can you. So it's made me think an awful lot differently." (PA20)

Many patients discussed how their personality type and/or keeping active and maintaining normality helped them to accept and cope with their disease and treatment. Some reported being proactive, positive and strong willed, which helped them to view things more positively and continue with their normal lives:

"A lot of it is up in your mind I think. Maybe that's why I try to keep really positive and get on with stuff." (PA15)

Keeping active, usually in terms of working and recreational activities, as a way of coping was also discussed by some patients:

"Well I kept going. You just have to. I still do quite a bit of running because I got back into running in a relatively big way so I'm actually quite fit." (PA32)

Finally, patients were asked during the interview how they would advise a close friend or relative if they too were diagnosed with CML. On the whole, patients' advice showed an awareness of worry at diagnosis and mostly reflected their own experience of how they had dealt with the disease. The main message from patients were positive: '*don't worry*' and '*keep going*'. Advice to others included to forget about it or to talk about fears with someone else. The advice PA04 gave mirrors how she spoke about her own treatment in positive terms:

"Look at me I'm here after all these years, you know, and try not to worry too much. These drugs now are amazing. I would be very positive and try and put their minds at ease." (PA04)

A second message from patients was to keep active and keep going. Again, this reflected the positive attitude patients held themselves. The words used about this seemed to suggest that despite patients' positivity, there may still be a struggle involved in remaining active. Patients advised: '*don't give up*' (PA28), '*don't let it get you down*' (PA15) and '*accept what your life is now...you have to*' (PA25), suggesting a determination and psychological effort in the process of coming to terms with

the disease, rather than this taking a passive course. PA30 had a very active life working full time in a senior position, doing voluntary work and pursuing hobbies. Her words also suggested that despite this, it had taken a conscious decision and a marked effort to maintain this level of activity:

“It’s like anything you have to try and, you’ve got to understand that you’ve not got to let it manage you.” (PA30)

Negative or uncertain perspectives on life

Despite positive comments from most patients about how they accepted their disease and viewed life after diagnosis, several of the same patients also expressed more negative or uncertain feelings regarding their life since diagnosis. This suggests they may not be simply negative or positive about their disease, and indeed may switch between the two. Some commented on their fear of disease progression, death, and contracting an illness which meant TKIs were contraindicated:

“So in the back of my mind it’s always, well cancer will get me eventually. Not just now thanks very much. But I know you can go on and live a normal life and in your head you know that for a fact but in your heart, it’s always the elephant in the room and when you get really ill, I do get a bit like, oh god.” (PA30)

Such anxieties regarding their future health were also seen in the thematic synthesis. There was also a reported heightened anxiety over general health. PA27 was diagnosed several years ago and talked about keeping active and ‘*getting on with it*’ but also described himself as a ‘*worrier*’:

“Just if I’ve got a high temperature, if I’ve got a bit of a woolly head which she [CNS] knows about. If I’ve got a chest infection I do tell her and she [CNS] makes a note of it and everything.” (PA27)

PA20 talked about how her anxiety was raised around the time of outpatient appointments:

“I do get a little bit worked up before I go, I think because I forget about it the rest of the time and it’s always just on your mind that it could, you know, it might not be as good as it was last time.” (PA20)

Some patients expressed uncertainty about their prognosis:

"I mean if I asked them, you know, how long would I be able to carry on going? I don't suppose they know really because everybody is different." (PA15)

Others spoke about their concerns due to co-morbidity or the ageing process, rather than CML. PA19 talked about how he had little hope of his kidney function improving:

"I think it's at 22%. I'd like to see it go up a little bit but we don't know. I'm doubtful. I think it will stay around the lower 20s." (PA19)

PA02's view of his prognosis was influenced by the loss of his wife:

"I've got nothing around to...worry me, my wife died so, the quicker it comes the better you know...that's it." (PA02)

Hopes for the future

When patients discussed how they hoped to see their future, they expressed what may be viewed as modest aspirations. Patients reported hoping their disease would remain under control:

"...as long as this drug keeps working for me, I'm quite happy to take any side-effects that come and they will, you know, providing I can still function independently then I'll be quite happy." (PA25)

PA15, a middle aged man said he wanted to live '10, 15 years or more' years, and PA30, a similar age, wanted to live to a 'normal age', and PA04 wanted to 'die a painless death'. PA06 considered donating her body to medical research. PA24, who previously reduced his medication dose on the advice of an alternative therapist, was the only patient to mention a desire to stop his medication in the future:

"I mean to be fair I would like to go even further and see what happens if I stopped taking them but if I did that then it would have to be under a controlled environment really." (PA24)

5.4.3 Summary of theme 4

On the whole it seems patients held a good level of awareness in several areas of their disease and treatment however there was variability and it was clear that levels of understanding could not be

presumed both between and within individuals. Patients may hold significant misunderstandings about aspects of their disease, such as fear of passing on CML to their children. Even where there seems to be a good level of awareness, such as disease response, patients understood this in different ways. Areas of particular concern or lack of awareness were around side-effects and the causes of CML, mirroring previous findings in *theme 3 (hospital care good and bad)*, regarding patient-practitioner communication. Some patients felt little need for information and knowledge and were reluctant to search the internet, whereas others found this valuable, and written information was regarded as beneficial on the whole.

A common experience to most was the shock felt at diagnosis and patients commonly described a process of acceptance of their diagnosis and a return to daily life activities. Rather than this acceptance being a passive process it seemed to occur as a result of learning more about the disease and treatment and seeing their TKI medication working successfully. Many patients reported a positive approach to their disease, sometimes put down to personality type and keeping active. Several interviewees also expressed a feeling that they felt “lucky” to be alive. When asked what advice they would give others newly diagnosed with CML, patients discussed remaining positive and active, but revealed that emotional effort and willpower was required for this, which perhaps helps to explain why several of the same patients also reported negative ideas and fears for the future, a struggle reflected in the thematic synthesis.

This theme has demonstrated the importance of understanding that patient levels of knowledge and awareness of their disease and treatment is likely to be individual and cannot be estimated or assumed. Furthermore, despite many patients describing positive perspectives on their life with CML, this may be on a background of anxiety and psychological struggle, and emotional support may be required to maintain such positivity. The final section, *theme 5*, describes how patients managed their disease and medication. I hope to show how this is influenced by the impact of treatment both physically and on day to day life, by external influences of social support and hospital care and also by those internal variables described here in terms of disease knowledge and awareness, and a likely changeable and mixed perspective of their disease.

5.5 Theme 5: Managing the disease is individual

This theme outlines how patients made decisions about their medication and symptom management. It attempts to draw in the influence of the themes already described and show that what may seem a simple process of taking a tablet once or twice a day, actually represents a complex decision, influenced by many other factors.

Adherence

A large proportion of the group reported having missed their medication at some point, or not taking it as directed in terms of dose or timing. Many had not taken their tablets as prescribed infrequently: less than once a month, and for some it was more frequent: once a month or more. However, none reported having missed their tablets more than three times a month. Mostly, patients could not be specific about exactly how often and when they had missed their tablets as PA04 reported:

“No probably not even that. Probably in a year I’ve probably missed perhaps 3 times, you know 3 tablets.” (PA04)

Furthermore, their language showed they generally viewed missing medication as a rare event:

“Yeah but not very, it’s only once in a blue moon really is, you know, they’re second nature to me.” (PA26)

There were also accounts from patients who had never missed their medication, some of whom also reported they had not taken their medication as prescribed at some point. Of these patients, accounts included taking medication late but not missing it, being instructed to miss medication by a doctor but not missed it otherwise, and PA24 who had voluntarily cut his dose although had otherwise never missed his medication (*see theme 3 hospital care good and bad: communication*). Of those who simply had never missed any medication, they suggested this was down to their memory, a matter of never forgetting:

“No it’s not difficult to remember and I know I’ve got to take them because it’s in my mind to take them. I don’t forget to take them.” (PA27)

Reasons for not taking medication as prescribed fell into intentional and non-intentional categories. Most reported unintentional reasons, commonly forgetting their medication, and looking further into what patients said, this was often related to different triggers, the most frequent being a change in routine, expected or not, causing patients to forget their medication:

“I’ve got a camper van and we go away at the weekends, take the grand kids, they’ll have probably been late tea and I’ve forgot my tablet.” (PA15)

“Sometimes I’ve gone round to my sister’s and I haven’t took them with me and then we’ll decide to have a drink and then I end up staying the night.” (PA06)

The timing of when patients forgot their tablets then had a bearing on whether they took them late or missed the dose. Some patients reported that if they had missed taking their tablet with their meal and then had eaten, they had to omit it, as they wouldn’t be taking the TKI as directed, or it would cause nausea and sickness:

“I would try my best but sometimes, you know, inevitably you’d be, “oh I forgot my tablets” and then about 10 minutes later you would be eating or you might have eaten something.” (PA32)

“On occasions when I’ve forgotten to take it, I’ve decided now not to take it that day because if I take it without doing that, without sandwiching it within my food, it will make me feel sick.” (PA04)

Other reasons reported for forgetting were being unwell and taking multiple medications:

“Aaah...I’ve got that many tablets, yeah. I mean I’ve got tablets for my blood pressure, tablets for everything.” (PA02)

Finally, PA21 was the only patient to describe a more external reason for unintentional non-adherence; running out of medication:

“They haven’t purposely not given me the right amount but the last time I went to see Dr [consultant name] there was a stand-in doctor and he didn’t quite give me enough medication, so I had 3 days where I didn’t take it.” (PA21)

PA21 was reassured by her consultant that missing 3 days was not concerning as discussed in *theme 3 (hospital care: good and bad: hospital system)*. However, it is interesting to note that PA06 also described this scenario, but she phoned her hospital team who quickly arranged a new prescription, meaning she didn’t miss any medication.

Less frequently patients reported not taking their tablets as prescribed due to intentional reasons. This could be due to advice from practitioners not to take their TKIs as a result of illness: gastrointestinal bleeding and post-surgical complications described by PA19, significant co-morbidities (PA28), and allergic reaction:

“Proper allergic reaction. I was up at the yard and they were saying, you look a bit swollen and somebody there had a nursing background and said, I think you really should go to A&E. So I went down to A&E and they took me off it.” (PA30)

Others took their own decision to miss/reduce their medication. PA29 reported missing her medication intentionally to avoid nausea at her son’s wedding:

“Like when my son got married and I were going for a meal, we stayed in a hotel and we had a meal and I thought I really want a glass of wine, you know, when you’re mother of, not mother of the bride, mother of the groom, and I thought do I really have to take that?” (PA29)

PA24 intentionally reduced his dose on the advice of his alternative practitioner (described in *theme 3 hospital care good and bad: communication*), as he felt his concerns about fatigue weren’t listened to by the CNS:

“...she said to me, why don’t you cut down your medication and see what it does? So I did and I didn’t tell [CNS name] for ages.” (PA24)

Finally PA25 described intentionally missing medication as she had a sickness bug:

“Only once and it was when I had a sicky do and to this day I don’t know what caused it.” (PA25)

Strategies to support adherence

Strategies to support adherence were described by all patients and were mostly aimed at aiding memory. Some used multiple prompts. Common strategies were linked to a daily routine, often taking tablets around specific mealtimes, but also when going to work or having a bath. PA27 described using these prompts with the more complicated nilotinib regime:

"Yeah I take it before my tea you see, when I leave work but in the morning I take it when I get to work just about maybe an hour and a half I've been to work and then I take them." (PA27)

Mealtimes not only acted as a prompt but could protect from GI side-effects which were common and impacted on daily life (see *theme 1, sub-themes: symptoms, side-effects and varying treatment success, and daily life is changed*), adherence for some depending on the timing of meals due to these side-effects, as discussed earlier in this theme. In addition to acting as a prompt, patients were often directed to take medication after or prior to mealtimes. PA11 described the instructions he was given for imatinib:

"I always remember that one because I have it with my dinner at night. You've to have it before you go to bed, an hour before at least but they advise you to take it with food." (PA11)

Polypharmacy was referred to patients as both an aid to remembering to take their tablet and as part of their routine for taking other medication:

"... just have them at the side of my bed and I have some other medication, so other things are in there." (PA06)

Several patients talked about how close family members supported their adherence, reflecting the importance of social support (*theme 2 social support level and type matters*). This involved relatives asking patients if they had had their medication, reminding them to take it, bringing it to them when they had travelled and forgotten it, providing devices, and carrying a supply themselves:

"...with nilotinib I kept some in that car, car in [city], [wife's name] carried a bit in her handbag because sometimes if it's not in that little green thing I've probably not got any on me but she'll have her handbag she'll have a strip in her handbag." (PA32)

Other strategies included setting an alarm, using a device (such as pill box, tube or carrier) and also carrying an extra supply in a work bag. PA20's alarm went off during the interview:

"That's one of the signs...that's me tablets, that's me alarm, six o'clock and six o'clock (goes into kitchen to take tablets then comes back into living room)." (PA20)

Supported by his consultant, PA32 built up a 'buffer' supply of medication which helped as he worked away from home, so getting hold of prescriptions could be difficult (see *theme 3 hospital care good and bad: health system*):

"I've got the issue of making sure I've got tablets in the right place which eventually we cracked by having a slight buffer in the supply of nilotinib. So I built up a buffer so enough to cover me in both places." (PA32)

Effect of missing medication

A small group of patients reported no physical effects from missing medication, all of whom described unintentional non-adherence, with one feeling side-effects if he took the dose late. Several patients reported that they felt missing an occasional dose hadn't or wouldn't affect their disease response. These patients implied that they felt missing their medication, or not taking it as prescribed, wasn't a cause for concern, as in the past this hadn't made them unwell or effected their response:

"Very rarely does that happen but if for any reason it does, I leave it that day. I don't think one day within a month is going to make any difference." (PA04)

Accounts from some patients were perhaps more concerning: PA24 who reported cutting down his dose without initially discussing it with clinical staff (see *theme 3 hospital care good and bad: communication*), PA21 who missed three consecutive days due to a prescription error and was reassured by her consultant that this was acceptable, and PA30 who missed medication occasionally and said she *"would quite confidently not take them for a week"* if she was away. Others seemed less certain of the effect of missing medication, explaining they wouldn't know what to do in this situation or they were unaware of the impact this would have on their disease:

"Well I didn't do it very often and overall I don't think it made any, I didn't have any immediate side-effects of it. Whether it impacts on the BCR-ABL levels I don't know." (PA32)

As mentioned in *theme 4 (sub-theme 1 disease knowledge and awareness varies)*, there was no data to suggest patients were explicitly informed their tablets should always be taken as prescribed, perhaps as there is an implicit understanding of the importance of this in the context of controlling cancer. Furthermore, and as also seen in *theme 4 (sub-theme 2 perspective on life is changed)*, patients revealed this understanding when referring to their positive perspectives on the disease:

“...think it’s like having, I presume it’s like having diabetes. If you know you’ve got to have it every day, you do it don’t you.” (PA04)

“...as long as I keep taking the tablets I’m fine.” (PA11)

However, looking into the earlier sub-theme: *disease knowledge and awareness varies (theme 4: individual influences)*, it seems there may be a lack of understanding among some patients, which could impact on adherence, some expressing misunderstanding around prognosis, side-effects, and the prospect of stopping TKIs in the future. Whilst some showed an implicit understanding of the need to regularly take medication it is questionable whether all patients fully understood their treatment, the need to take it as prescribed and the impact of not doing so.

Managing adherence and side-effects independently or with professional advice

There were some recounted instances where patients had a discussion with their doctor about a missed or reduced dose of tablets. Differing advice was given in each occasion, ranging from general advice to more specific instructions on what to do next. As discussed (*theme 3 hospital care good and bad: hospital system*), PA21 was advised it wasn’t a problem to miss three tablets in a row, while PA30 and PA06 were advised by doctors that they weren’t worried about them missing doses “*now and again*”, and that it’s “*not a good idea*” respectively:

“I have told Dr [consultant name] that I do sometimes miss it and he said, well it’s not a very good idea to miss them but it’s not affected anything.” (PA06)

PA24, who voluntarily cut his dose and initially didn’t tell his CNS, was eventually advised by his CNS to continue on the lower dosage, and PA15 recalled the more specific advice he was given:

“As I say, I’ll say I’ve missed a tablet what do I do? He said well don’t take two just take another one the following day, it’s up to you when you take it.” (PA15)

Others however, reported that they hadn’t talked about missing tablets with their doctor or nurse. The thematic synthesis also found some underreporting of non-adherence. Reasons provided by patient interviewees were either that they felt well, their disease response wasn’t affected, they felt it was too infrequent to be important or, as PA32 explained, he didn’t want to bother the doctor, feeling it was his own responsibility:

"...it's really on me, for me to manage it. He doesn't need me whinging on about it (laughs)". (PA32)

PA24 pointed out that he would have discussed his intentional non-adherence earlier if his BCR-ABL results had become concerning:

"If she'd have said at the blood test, look it's going wrong there, then I would have probably confessed but I didn't confess. I did confess in the end." (PA24)

Variability was also noted in the frequency with which side-effects were reported to clinical staff, with patient accounts of methods to manage these independently, particularly muscle cramps (*theme 1, sub-theme 1 symptoms, side-effects and varying treatment success*), alongside fatigue, nausea, diarrhoea, indigestion and temperature sensitivity. Patients either took over the counter remedies, did some muscle stretching or simply learned to cope, as described by PA30, with reference to significant nausea and vomiting:

"Just carried on, and they'd say, how's your sickness and I'd say, it's alright, a bit sick now and again. I've not been so bad, I'll be right. So I always used to struggle with being sick but now I can just be sick and it's fine, it's not a problem." (PA30)

Some suggested a hesitancy to discuss side-effects with their clinical team, because they perceived their doctor to be too busy, they felt they could cope, or they were reluctant to take further medication, if offered:

"I cope with a bit of cramp that I get because I just think there's no point in putting even more drugs in my system you know." (PA21)

As seen in *theme 3 (hospital care good and bad: communication)*, some (including one of the hesitant five) also reported that their doctor or nurse wouldn't or couldn't listen to their concerns about side-effects:

"I do say stuff over the phone but I often think it just falls on deaf ears and just think, yeah that's par for the course really and that's it" (PA24)

Finally, PA24 and PA29 saw an alternative therapist, who achieved successful outcomes in treating fatigue and pain:

“She said basically lavender, chamomile and try this and this in your bath and I said is it okay to take with this drug? I was in that bath twice a day and I didn’t take one steroid tablet. It went. I stood it out and it went eventually.” (PA29)

The thematic synthesis also found patients did not always report side-effects. Despite some reluctance and difficulty in reporting, several patients, including some of those who self-managed other symptoms, also reported incidents when they had received advice from their doctor or nurse about side-effects. More commonly, patients seemed to discuss nausea with their practitioner, and were advised on changing the time of taking the medication, prescribed supportive medicines or switched to a different TKI. For example, PA21 who previously suggested she could cope without professional help for her muscle cramp, had discussed nausea with her doctor:

“I like to take them after my tea at night really and that was the doctors suggestion, you know, to take them at night after your main meal is a good time because if you are feeling a bit queasy or whatever, it’s best at night rather than during the day.” (PA21)

5.5.1 Summary of theme 5

Despite none of the patient group reporting missing their medication more than three times a month (a level of non-adherence which could have a significant effect on BCR-ABL levels, as suggested by Marin et al, 2010), most reported missing their medication at some point, often due to unintentional forgetfulness. Mealtimes appeared to help prevent this type of non-adherence, acting as a reminder and being linked to protection from GI side-effects. Eating also impacted on whether and when to compensate for forgotten doses, some not taking the missed tablet, once remembered, due to the risk of sickness or not complying with guidance. Other strategies used by patients to aid their memory included; polypharmacy, use of a medication device or alarm and the actions of family members, reflecting the earlier theme highlighting the value of social support. Unintentional non-adherence rarely occurred due to external reasons (e.g. prescription running out) and compensating for this could depend on hospital systems, practitioner advice and their ability to provide extra medication quickly.

Intentional non-adherence was less common and could be on the advice of a practitioner, but also a decision by the patient in order to avoid side-effects. Despite the level of reported non-adherence being low, the potential for a clinically significant level of non-adherence was present for most patients as most reported forgetting their tablets at some point. Furthermore, compensating for a missed dose could be complicated by GI side-effects and related medication directions, which may

be difficult to discuss with a practitioner. This compensation was also affected by the patient's perspective on the impact of a missed dose, with several not concerned about this due to the lack of impact on their BCR-ABL levels, or not experiencing any ill effects, and some not reporting missed doses to their doctor or nurse for the same reasons or not seeing it as important enough to report to their practitioner. Self-management techniques were sometimes used to deal with side-effects, which is perhaps concerning considering the hesitancy, difficulty, or lack of reporting of such side-effects to practitioners, as described by some. Lack of reporting of non-adherence and side-effects was also evidenced in the thematic synthesis. Several of the patient group did, however have some discussion with their doctor or nurse about side-effects, often GI symptoms, although the other most common side effect, muscle cramps, appeared to be less likely to be discussed.

This theme demonstrates that non-adherence is common and has the potential to impact on treatment response. Adherence and compensating for missed doses is complicated by side-effects and the patients' perspective, and can be supported by the hospital system, practitioners, and family in different ways, reflecting earlier themes. These factors can in turn impact on the patient reporting and practitioner discussion of both non-adherence and side-effects.

5.6 Chapter summary

Thematic analysis of the interview data has shown that CML side-effects were common and impacted on the daily life of most patients. Considering such effects may be experienced over the entire life-course, it is likely they could have a significant long-term impact on quality of life. However, as treatment is successful for most and therefore essential, other ways of modifying this impact need to be considered. Social support, relationship with practitioners and organisational aspects of care were found to buffer the impact of CML. Social networks, for example, offered emotional support, advocacy and practical help. Aspects of hospital care included the caring and reassuring nature of practitioners, and the patient's ability to talk freely. Patients appreciated clear explanations from practitioners, and it is somewhat worrying that several found it difficult to discuss their concerns about symptoms and side-effects. More practical problems included missed or delayed tests, test results and/or outpatient follow up letters, long outpatients' waits and difficulties with pharmacy systems.

Patient's disease knowledge and perspective on life ultimately also affected their self-management of CML and treatment side-effects. Despite awareness regarding several areas of disease and treatment, patients may hold some significant misunderstandings and there was a particular lack of awareness around side-effects and the causes of CML. Notably, knowledge and awareness varied within and between patients, with some preferring less information, or different formats. A uniform

method of providing information may therefore be inappropriate, with individual approaches that consider patient knowledge more suitable. Patients commonly described having a positive outlook to their disease and feeling “lucky”; however further analysis demonstrated the emotional effort and willpower this required, with nearly half also describing negative feelings and fears. Disease acceptance was a dynamic rather than passive process, involving learning about CML and keeping active. Practitioner awareness of this may enhance their relationship and communication with patients.

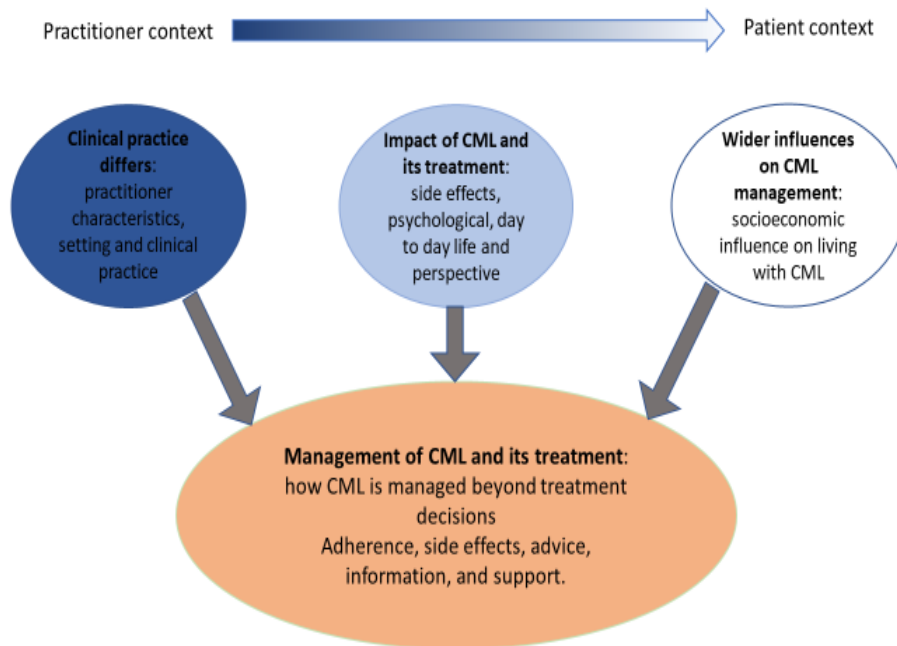
The influence of disease impact, social support, hospital care, disease knowledge and life perspective play out in the final theme, describing how patients manage their disease, with a focus on adherence and side-effects. Despite low levels of reported non-adherence, the potential for clinically significant non-adherence was present for most. Unintentionally forgetting medication was common even though all patients used a range of strategies to support their memory. Intentional non-adherence could result from practitioner advice, but also be related to side-effects. Compensating for missed doses was closely tied to GI symptoms, mealtimes and medication directions. Difficulty or hesitancy discussing side-effects with practitioners or lack of awareness, may further add to this complexity, as is reflected by several patients reporting their self-management of side-effects. Furthermore, some were unconcerned about missed doses, which could result in not reporting this to clinical staff, meaning practitioners may be unaware of non-adherence. Encouraging the reporting and discussion of adherence and side-effects has the potential to impact on quality of life and disease response. Considering all the factors influencing the way patients manage their disease may contribute to the success of discussions. The following two chapters describe the thematic analysis of practitioner interview data, and a further chapter then considers the two analyses together, alongside wider literature.

Chapter 6 Practitioner interviews 1

The following two chapters describe thematic analysis of the practitioner interviews, in order to examine experiences of managing patients with CML. Practitioner accounts add context to the patient interview analysis, detailing how their perspective and the realities of service delivery may have impacted on the management of CML patients. This helps to achieve my final aim of producing findings which are relevant to practice, and also adds validity through triangulation. Four analytical themes were defined following analysis: *clinical practice differs*, *impact of CML and its treatment*, *wider influences on CML management* and *management of CML and its treatment*. The first chapter will present theme one which provides a contextual background to the practitioner setting, and the second chapter describes the other themes.

The thematic visual map shown in figure 15 represents the practitioner themes and how they interact. The first chapter focussing solely on *theme one; clinical practice differs*, illustrates the role of the practitioner in managing CML from their own clinical perspective and within their own hospital context. It provides a description of interviewee characteristics including their hospital type, specialism and patient population. Clinical decision making is discussed, and despite variation in their characteristics, practitioners seemed to agree on the main influences on this process. Attributes of outpatient care are then considered. There seemed to be a common view that patients with CML were generally seen as being a small part of their overall workload, and less complex than other haematological malignancies. The second findings chapter however, provides evidence that practitioners were also aware of the perspective and context of patients living with CML. In *theme two: impact of CML and its treatment*, practitioners describe CML in terms of its impact on daily life, side-effects and patient outlook on life. They also explored the patient's socio-economic context and how this may affect their management and outcome in *theme 3: wider influences on CML management*. The visual map (figure 15) represents this breadth of perspective, ranging from seeing CML within their own workload to viewing it from the patient's perspective and within their context, as a bold arrow at the top of the figure. The visual map suggests that each theme influences the way practitioners manage patients with CML, as is explored in *theme 4: management of CML and its treatment*.

Figure 15: Practitioner interview analytical themes



6.1 Theme 1: Clinical practice differs: practitioner characteristics, setting and practice

Theme 1 provides an overview of the care delivered to CML patients in the YHHN region.

Practitioners interviewed were more likely to have an interest in CML due to the snowball sampling process (identification of key practitioners with an interest in the thesis topic), which raises expectations of consistency in clinical practice characteristics. However, this was not the case as differences were seen in the experience and specialisation of practitioners, as well as in clinic set-up for CML patients, as can be seen in Table 7. Practitioners also described the different factors influencing their clinical decisions, and variations in the characteristics of the outpatient care they provided. Some quantification of findings is provided in subtheme 1 (practitioner experience, role, practice and clinics) in order to provide a clearer picture of the care provided to CML patients within the YHHN region. Each practitioners' clinical context provides an understanding of how *the management of CML and its treatment (theme 4)* may be influenced by differences in clinician characteristics and service provision. While patients told individual stories in interviews, practitioners provided a perspective of CML management within the complexity of care provision across all their haematology patients. From sub-theme 3 onwards, I start to bring in some of the

findings from the patient interviews where appropriate, in order to build a fuller picture of patient care.

6.1.1 Sub-theme 1: Practitioner experience, role, practice and clinics

Practitioner experience and role

Of the thirteen practitioners interviewed, all were in a specialist post; seven haematology clinical nurse specialists (CNS) and six haematology consultants. Practitioners reported a caseload of between 10 and 52 CML patients under the care of each hospital, with greater numbers in the two cancer centre hospitals and fewer at local hospitals, although two of the latter treated between 40 and 50 people. CML patients were rarely admitted and most received outpatient care. Around two-thirds of the practitioners had practiced in haematology for at least ten years, with five to 33 years' experience in their specialist role. PR06, an experienced consultant reflected on how CML treatment had developed during his career:

“It has changed hugely. I mean if you’d been seeing someone in their 20’s with chronic myeloid leukaemia when I started in the mid 80’s, you really were looking at a transplant, you know, we didn’t have an effective treatment beyond Interferon, hydroxycarbamide which weren’t guaranteed in any way to prolong life really.” (PR06)

Four practitioners were relatively new to their role having between one and five years as a CNS or consultant. PR08, a new CNS, explained how she felt daunted by her CML caseload and referred back to the consultants quickly, due to her inexperience. These characteristics and others are displayed in table 7.

Table 7 Practitioner characteristics

ID	Role	Experience in role	Hospital type	Specialism	OPA clinic type
PR01	CNS	10 years+	Cancer centre	Myeloid +/- CML	Specialist CML
PR02	Consultant	10 years+	Cancer centre	Myeloid +/- CML	Specialist CML
PR03	CNS	10 years+	Cancer centre	Myeloid +/- CML	Specialist CML
PR04	CNS	10 years+	Local hospital	Myeloid +/- CML	General haematology
PR05	CNS	10 years+	Local hospital x 2	Myeloid +/- CML	Specialist and general haematology
PR06	Consultant	10 years+	Local hospital	Generalist	General haematology
PR08	CNS	1-5 years	Local hospital	Myeloid +/- CML	Specialist CML
PR10	Consultant	10 years+	Local hospital x 2	Myeloid +/- CML	General haematology
PR11	Consultant	1-5 years	Local hospital	Myeloid +/- CML	General haematology
PR14	CNS	10 years+	Cancer centre	Myeloid +/-CML	Specialist CML
PR15	Consultant	1-5 years	Local hospital x 2	Generalist	General haematology
PR19	CNS	10 years+	Local hospital	Generalist	General haematology
PR20	Consultant	1-5 years	Cancer centre	Myeloid +/- CML	Specialist CML

Type of hospital and practitioner specialism

Almost one third of the group worked at a hospital with a cancer centre, with the other two thirds practicing at local hospitals without a specialist centre. This reflected the proportion of hospital types where interviewed patients were cared for and the split of centres in the wider YHNN population. However, within these settings, roles differed. Ten of the thirteen practitioners had a formal role caring for patients with myeloid malignancies, which included CML, and/or had a specific

interest in caring for people with CML. This group included CNSs who specialised in myeloid malignancy, or ran nurse led CML clinics, and a remote monitoring clinic. The consultants in this group had a particular interest in CML, which included setting up a registry of patients with the disease in their own hospital and running a CML clinic specifically for teenagers and young adults. One also had the role as regional lead for CML, which involved responding to queries, networking nationally with other specialists, and disseminating information locally, in addition to work as a consultant haematologist:

“It’s just more work [laugh] but it’s a more enjoyable workload so it’s carving out extra bits of time.”

Three practitioners described themselves as more generalist in terms of their practice, seeing patients with a range of haematological malignancies and disorders. PR06 emphasized the need to be aware of how this generalist role may impact on expertise dealing with a specific disease such as CML:

“We’re never going to build up the bulk of experience in CML with somebody in a centre like [cancer centre hospital] or [city hospital outside of region] who actually takes a specialist interest. So, you’ve got to be humble.” (PR06)

Differences in outpatient follow up and inpatient care

Data regarding the type of outpatient follow up was gathered from twelve of the fourteen hospitals in the YHHN area. Unfortunately, it was not possible to secure an interview at two local hospitals, despite several attempts, and a decision was made that it would be inappropriate to keep contacting the practitioners there.

Across the region there was considerable variation in the outpatient service delivered. Four hospitals ran a CML specific follow up service. This included the two cancer centre hospitals, which provided a service specifically for teenagers and young adults, a nurse led telephone clinic and a CML clinic run by the regional CML specialist. Despite having fewer patients, two specialist CML services were provided in local hospitals, including a nurse led telephone clinic and a CNS led CML outpatient clinic:

“What we are now at the moment doing, we are looking into some Trust policy for CML patients, their management which can be then basically used in nurse led clinic, so basically indication criteria, exclusion criteria for nurse led clinic who can be referred, then refer the patient back to consultant, yes.” (PR11)

At the remaining nine hospitals (all local) patients with CML were seen alongside those with other haematological malignancies. In contrast to the examples above, this was seen as a practical solution by PR06 and PR10, who worked in local hospitals with a smaller caseload of CML patients:

“...in a little DGH [District General Hospital] where it’s a minority of patients, it’s a rare disease, so we couldn’t, practicality we couldn’t have a CML specific clinic here.” (PR10)

There were further differences in whether practitioners treated inpatients. Although few CML patients were admitted, this may have a bearing on how clinics were set up and practitioner experience. Practitioners at the two cancer centre hospitals cared for patients as outpatients and inpatients, however practitioners at some local hospitals rarely or never saw inpatients, either because the hospital didn’t provide intensive chemotherapy requiring admission meaning patients were transferred elsewhere, or for two CNSs, care seemed to be set up that way:

“We don’t get too necessarily involved with the inpatients other than knowing what’s going on with them really, because obviously doctors do a ward round every day. But we do tend to dip in at the beginning of the week and the end of the week just to see where we are with those patients.” (PR19)

Multi-Disciplinary Team (MDT) meetings and differences in local population

Some practitioners discussed how MDTs were set up and used, and differences in their patient populations. Some hospitals worked collectively in larger MDTs whereas others worked more independently:

“[I am] not involved in MDTs other than the [cancer centre hospital] group, [three local hospitals] group. I mean I don’t have a lot of contact with the [cancer centre hospital outside of the MDT] area, they tend to stay quite autonomous in what they’re doing.” (PR02)

PR20, expressed concern about two hospitals who participated in their MDTs:

“...although they’re one Trust, have different clinicians working in very different ways at each site, so there is often concern or anxiety from them who don’t see as many of these patients about how to do things, so they, I think probably bring more people back more often [to the MDT]” (PR20)

PR01 also described how hospitals from outside the HMRN region fed into the MDT at their cancer centre hospital, and like PR20, suggested that ‘simple’ checks hadn’t been carried out before bringing the case to MDT:

“We get regional referrals that are coming in as well and, you know, they say, oh this lady is, you know, she’s never been. ‘Have you checked compliance?’ ‘Oh no we haven’t’ type of thing. ‘Well just make sure she’s taking it’, you know, before you start chopping and changing her drug around.” (PR01)

As mentioned earlier, in-patient populations vary depending on whether the hospital can provide intensive chemotherapy. Further to this, the geographical population served by the hospital may lead to differences in the CML caseload:

“So [place] has a different cohort of patient, probably a bit more elderly patient. With [an] ageing population you get more co-morbidity and also that clinically guides you [about] what sort of inhibitor that you are going to choose, so it is definitely something [that] what would influence your practice.” (PR11)

“...we’ve got quite a big TYA [Teenager and Young Adult] contingent, we must have about 10 under 25 patients, so they’re a bit more obviously tricky because they’ve got other life things going haven’t they.” (PR14)

Primary care involvement

Around half the group discussed the involvement of GPs in patient care. This was in order to optimise the management of cardiovascular side-effects of some TKIs, for co-prescribing purposes in people with co-morbidities, or to help contact a patient who had been declining appointments and treatment:

“I think one of the things we do understand is people who are on tyrosine kinase who have got cardiac risk, then you have to ask the GPs to manage the patients as well.” (PR06)

“But we’ve written to her telling her she’s putting her life in danger in words of one syllable. The clinicians have written to her. The GP has tried to physically find her, but you can only do so much.” (PR05)

PR03 recounted negative experiences of working with GPs. In one case the GP and patient made the decision to stop TKIs due to abdominal pain, which was interpreted as a side effect, without consulting the hospital team:

“So between her and the GP she’d stopped taking the imatinib, only for a couple of weeks, then she got in touch with us, she was still getting the abdominal pain, not as much, but she still was. Anyway they sent her for a scan and they discovered that she’d got renal cancer. So we then fetched her into clinic and, well they restarted her on the imatinib because they felt it wasn’t that that was causing the abdominal discomfort it was this renal cancer.” (PR03)

6.1.2 Sub-theme 2: Factors influencing clinical decisions

Of all the topics discussed, this sub-theme holds the most amount of data from the practitioner interviews, perhaps reflecting how clinical decision making is viewed as a crucial part of the role. These decisions were commonly treatment related, involving choice of therapy, management of response, toxicity and tolerance of drugs, and the possibility of stopping TKIs for some patients.

Practitioners described switching TKIs due to side-effects or poor response, some implying that these problems could occur across all TKIs:

“...these drugs do have side-effects and if you’re convinced that a. it’s due to the drug and b. the side-effects are severe, you probably move them onto something else, dasatinib, bosutinib or ponatinib, there’s lots of choice, although they all have their own problems.” (PR06)

The importance of accurately assessing the patient before switching their medication was highlighted, which included consideration of cardiovascular risk, checking adherence, looking at other medications and precise molecular monitoring. Most practitioners referred to their practice of

three-monthly blood monitoring of BCR-ABL level, with some exceptions such as less often in the very elderly or more often in patients who practitioners were concerned about:

"...if it's somebody we're worried about we'll repeat it but if it's somebody we're not worried about we'll just leave it until next time they come back in 3-month time." (PR05)

The possibility of stopping TKIs was also discussed. Only patients who were hoping to become pregnant or had gone through a clinical trial to stop TKI medication, were reported to have stopped. Otherwise, this was considered a likely future change to practice. Practitioners' concerns around this included the lack of clear guidance on reducing/stopping, the raised cost of molecular monitoring and patient desire to stop:

"...there are some patients that are going to say, 'yeah, I'm not stopping. I don't want to think about that.'" (PR14)

Guidelines and clinical trials

Guidelines were considered a key influence on decision making. Many practitioners referred to using guidelines to aid clinical decision making for CML patients, several of whom reporting use of the European Leukaemia Network (ELN) guidance:

"...when they're newly diagnosed they come to face to face follow-up, diagnosis, sort of commencement of treatment, then we manage them in the out-patient following the ELN guidelines." (PR14)

Use of NICE guidelines for specific treatments was also reported in addition to the use of "guidelines" and "network guidance". The practitioner running the remote monitoring service used a local Standard Operating Procedure (SOP). PR04 however, whose role was more supportive than to make clinical decisions, explained why she did not use guidelines:

"I don't do any of the prescribing for the treatment but my role is mainly to support and so it's probably more, I really don't use any guidelines, it depends entirely on patient need really." (PR04)

The contribution of clinical trials, research and drug profiles to aid decision making were also referred to. Clinical trials and research gave information about TKI drugs, but PR01 also talked about research investigating medication adherence and side-effects:

“So, all the research is saying that these patients have low level symptoms that can then have an impact on adherence and outcome if you like.” (PR01)

Communication with colleagues

Most practitioners described communication with colleagues, at a local, regional, national and international level to support decision making. Commonly, methods involved discussion via MDT meetings and liaising with the regional CML lead consultant. Overall, practitioners described how communication with colleagues generally enabled the sharing of experiences and offered them reassurance in their decisions:

“I rarely make a very complex decision particularly if it’s something like a transplant decision without at least sounding out somebody else which is quite nice to be able to do that.” (PR02)

Practitioners reported using MDT meetings to discuss particularly difficult decisions, patients who were newly diagnosed, and those who had had a poor response or were struggling with side-effects:

“If people are struggling with imatinib or they’re resistant to imatinib or indeed nilotinib or the other 3 agents, then that would be discussed at the MDT.” (PR06)

Joint decision making through the MDT could lead to a sense of shared responsibility:

“We all decide together. Collective responsibility. The more brains the better.” (PR05)

Several practitioners also sought advice from the regional CML lead consultant, sometimes if ‘in doubt’ or if a decision wasn’t possible through the MDT:

“...if you get some difficult case then you have to bring it back to MDT and usually you’d discuss that with regional lead for CML.” (PR11)

Some also referred to working with individual colleagues within their hospital to facilitate decision making, including consultant haematologists, CNS colleagues, pharmacists and consultants from other specialities:

“...we work quite closely, because that is also advantage probably a bit of smaller Trust, because then you can basically discuss the patient with your colleagues from other specialities.” (PR11)

Practitioners also discussed support from colleagues at a regional or national level, including those with an interest in CML or scientists monitoring TKI response at the regional specialist blood laboratory (HMDS):

“So, we have the expertise and knowledge and anything that stretches that we go down the road to [city hospital] or [Out of Area city hospital] or up to [OOA city hospital] where the centres are slightly bigger than we are for further advice.” (PR20)

Working with GPs, clinical supervision, attending national and international conferences and a national CML working group were also cited by some as valuable in supporting their clinical decisions. PR02 explained that regional network meetings were useful for sharing information, however, a lack of practitioner time often prevented attendance:

“It’s difficult because people don’t have time to attend a lot of network meetings now, so we kind of know who each other are but it doesn’t feel that we get to meet up and link in as often as we used to.” (PR02)

Clinical assessment

Several practitioners also highlighted the use of clinical assessments and investigations to guide decisions. Often, practitioners discussed how co-morbidity and its interaction with older age and TKI side-effects influenced their choice of TKI and dosing:

“We’ve got some on hydroxycarbamide because they’re, I’ve got a 94-year-old lady who’s got CML and she’s not in a fit state to have imatinib really, so we just try and manage her carefully.” (PR14)

In addition to BCR-ABL results, risk scores also influenced treatment choice and clinical decision making, in particular the Q-risk cardiovascular score (due to the side-effects of some TKIs), and tests such as mutational analysis, hepatitis screening and chest x-rays.

Drug profile and availability

Awareness of side-effects such as cardiovascular risk, hepatitis reactivation, also speed and depth of response, and experience of using specific drugs were said to affect choice of TKI by some practitioners. PR20 described a young, fit patient who started on imatinib due to it having fewer side-effects (some practitioners regard the deeper, quicker response of a 2nd generation drug to outweigh the minimal, yet increased, risk of cardiovascular side-effects):

“I said ‘I’m going to put your daughter on imatinib’ and they looked at me and said, ‘no you’re not’. I said, ‘I am because of this, this and this’, and she’s responded really well and a year later she’s off at college and she’s had a major molecular response on imatinib and has no problems and they go, ‘you did the right thing’. But they wanted a second line drug because that was perceived as better and more expensive.” (PR20)

The availability and cost of various TKIs was also highlighted particularly as imatinib came off patent in 2016, therefore became considerably cheaper to the NHS:

“It’s not so bad with the imatinib because that’s off patent now, but we’ve still got nilotinib, dasatinib, we’ve got a lady on bosutinib. We’ve got somebody on ponatinib, so there are big cost elements to that.” (PR14)

6.1.3 Sub-theme 3: Set up of outpatient care

As discussed, the set-up of CML outpatient care varied across hospitals, and the practitioner group described positive and more negative aspects of this care. Attributes of care fell into the following categories: *services, structure, organisation and good practice.*

Services

In terms of services provided for patient care, several practitioners saw the HMDS specialist laboratory service as good quality, referring to it as “*superb*”, “*brilliant*”, and more specifically praising its reliability:

“The results are quite reliable, we get the results when we want the results.” (PR11)

PR20 also found the BCR-ABL response graphics provided by HMDS to be of value:

“HMDS who produce a nice integrated report with a graphical picture for me to say, this is where their BCR-ABL ratio is compared with previously and actually showing that to patients is really, really useful.” (PR20)

The HMDS electronic request form was appreciated, its clear results and comments if the patient’s response was suboptimal. However, some pointed out that HMDS results can take over two weeks to be returned, which could be after the patient’s outpatient appointment. This did not cause undue concern though, as systems were in place to ensure results were checked when available, or blood samples were taken earlier to ensure results arrived in time for the patient’s appointment.

The merits of the remote monitoring service offered by one of the cancer centres was also mentioned, in which patients do not visit the hospital, but have blood tests taken locally and complete a questionnaire, both of which are then sent to the cancer centre for analysis. The service is managed by a specialist nurse and senior scientist who review results and manage the timely dispatch of blood test kits and questionnaires. This was seen as offering a more convenient service, in agreement with patient interview data. Remote monitoring also offered a robust system for referral back into the outpatient system if major molecular response was lost (PR01, PR02, PR03):

“I think it’s more convenient. I think I would prefer it.” (PR03)

However, PR01 and PR03 raised issues with the service, including: lack of written information for patients about side-effects; potential issues with the stability of blood tests for biochemistry in the postal system; the need for patients to take responsibility for blood tests; and that patients may become ‘too remote’, making it difficult to monitor adherence:

“I’d like to think that those patients on the remote PCR testing are adherent but because you’re not seeing them and you’re not, asking them.” (PR01)

Hospital pharmacy services were seen as working well in one outpatient clinic, being quick to respond to problems and ensuring enough medications are in stock (PR05). Despite this, waiting times could be around an hour at the pharmacy and lack of adequate supplies of a particular medicine had occurred:

“We have to do 3 prescriptions because NHS England say you have to do one cycle at a time which obviously takes longer for us to do and then because it’s got to be remotely checked by a pharmacy, so we do get complaints that they’re having to wait an hour now for their prescriptions for it to go through the system.” (PR05)

Data from patient interviews was more prominent regarding problems with prescriptions, which could run out early or not contain the full supply. A home medication delivery service meanwhile, was seen positively by some with a specific interest in CML, which again reflects the patient interviews, however not all found it beneficial:

“We have a home delivery service for TKIs so patient basically get all their medication delivered which they find very helpful.” (PR11)

PR01 referred to a psychology service as good quality, although it had a prolonged waiting list:

“I don’t know what to do with the lady that won’t take it [TKI medication], but we’ve got a good psychology service here. The waiting list for out-patients is about 12 weeks.” (PR01)

Structure

The second category of ‘structure’ refers to the set-up of care and underpinning resources in the hospital. CML dedicated clinics were discussed by practitioners working in CML specific services. PR01 described the benefits of seeing the same consultant regularly in clinic, which matches patient reports:

“...they know they’re to see [consultant name], so for the patients it’s continuity of care.” (PR01)

PR20 talked about their Teenagers and Young Adult (TYA) clinic, which offered more specialist services:

“We tend to keep them [TYA] a bit longer partly because the young adults come with a bit more baggage and parents than the older patients, so they want that support a bit longer and then we also have access to a youth support worker which is great for getting them back into college, university or whatever they want to be doing.” (PR20)

Although CML specific services seemed to be viewed positively by most, some reported concerns with a similar spread of opinion to the patient interviews. PR14 and PR08 still saw a value in occasional face to face contact with patients from their nurse led CML phone clinics, either during annual reviews with the consultant or when they came to hospital for blood tests:

“To be honest tomorrow morning I can guarantee they’ll be 3 of them and I can see them go, “alright” [laugh]. So, I think, I like that really because at least they’ve seen me and I’ve seen them.” (PR14)

A number of practitioners expressed concern over a lack of time in outpatient clinics, having between 5 and 20 minutes per consultation, and CML patients sometimes having appointments in the same clinics as patients with more acute disease:

“If you have a busy clinic with lots of patients, lots of them take longer than 15 minutes, other diseases which are more complex have more complex chemotherapy regime. If you then have a stable CML patient in between them, it’s not uncommon to then kind of use this to make up time and I wouldn’t then sit there and prod and deep and look in between the lines. I’m quite happy to admit that when it’s, you know, an overstretched busy clinic.” (PR10)

This could mean patients not having the chance to discuss everything they want to including discussions about side-effects (PR01):

“Low level GI toxicity, you know, like feeling sick, people say they can burp and taste the Glivec. I don’t think we deal very well with that. Whether that’s because the patients are all mixed up with a really busy clinic and when they’ve waited an hour and a half to be seen, they just want to get out the door and don’t want to bring that up.” (PR01)

Providing time for listening and discussion resonates strongly with patient interview data which emphasized the value patients placed on the relationship and communication shared with practitioners. Even though attending a dedicated CML clinic, patients with CML could be seated in the same waiting room as people who are more acutely ill, as PR01 pointed out:

“All the patients sit in the waiting area together. So, there’s the acute leuks coming back after phase 1, 2, 3 of treatment and then you’ve got your CML patients coming back and you’ve also got your newly diagnosed.” (PR01)

PR14 and PR04 talked about the difficulty balancing calls to the nurse led phone clinic with the need to be present at appointments in the outpatient clinic:

“I always see new patients in the out-patient clinic just in and amongst the telephone clinic, so it’s not really ideal. We are putting together a business case for a new clinical nurse specialist, so that there will be 2 CNSs in that clinic.” (PR04)

Organisation

In terms of the organisational aspects of CML outpatient clinics, this mainly concerned preparing in advance. For the consultant working with PR01 (CNS), this involved checking who needed blood monitoring or risk scores, and reading through previous treatments:

“[Consultant] preps the clinic so [consultant name] preps all the CML patients before Friday, so [name] goes through them all. [Name] looks at all of the previous PCRs, [name] looks at all of the therapies they’ve been on. [Name] looks at everything like that and then when they come to clinic on the Friday, [name] sees them all.” (PR01)

Preparation can mean patients have a shorter waiting time in the outpatient clinic:

“Because I prep my clinics and I would generally say that my patients are usually seen either on time or within 20 minutes/30 minutes.” (PR10)

Patients were sometimes asked to have their blood taken a couple of weeks before clinic so their results were available at the outpatient appointment (PR06, PR10 and PR11). Where this practice was not in place, PR08 reported they had a robust electronic system to check results had been returned for all patients needing them. PR05 also sent a list of clinic dates to the pharmacy so they could calculate how much of each TKI drug would be required to dispense to patients on those days. Finally, PR02 explained that they offered flexibility with their outpatient clinic appointments, meaning patients could move their appointment and order prescriptions to accommodate holidays and day to day life:

“We will work around things to help with that and we’re quite often flexible with prescriptions and appointments to allow people to go away and that sort of thing.”
(PR02)

Efficiently run clinics and shorter waiting times were also highlighted in the patient interviews as a positive aspect of their health care.

Good practice

Elements of good clinical practice in ongoing CML outpatient care were referred to by PR02, PR06 and PR20, including continuity of care and psychological support:

“I think we’ve got better at realising you really need a holistic support for CML patients and hopefully they feel they can spill things out. I think we’re better at looking for cues for people who are not finding things easy and giving them time to hopefully share concerns.” (PR02)

Clinical expertise was also highly valued by patients. PR20 felt newly diagnosed patients were well managed by their hospital team, but that practice was not as good when switching TKI. The care provided by colleagues within their trust but outside haematology was also discussed by practitioners. PR11 emphasised the benefit of working with other specialities and PR03 expressed concern about other specialist’s lack of knowledge about CML treatment:

“For this woman when she was in [city] waiting for her ear operation, they were unsure whether she should have certain antibiotics, whether she should stop her imatinib. They really didn’t know.” (PR03)

Suggested improvements to outpatient care

Practitioners suggested ways in which outpatient care might be improved, which fell into the same categories of service, structure, organisation and good practice. Some discussed the possibility of remote monitoring. PR14 had been trialling this in their cancer centre, however felt that the process could be improved and stream-lined, as in the other cancer centre hospital:

“I think that would be nice if we could because I know in [cancer centre hospital] they’ve got their remote monitoring and I think that can all be done via a package and it’s all done that way...if we could get the monitoring to be less cumbersome perhaps, if they could get that done locally and that was something that was back more quickly I suppose that might help a little bit.” (PR14)

Interestingly, PR20, at the same hospital seemed unaware of the remote monitoring trial, and along with PR05 at a local hospital, felt that remote monitoring would benefit patients:

“That would be a good progress, get patients out of hospital because if patients aren’t coming to hospital then they don’t feel poorly.” (PR05)

PR05 believed CML telephone clinics would also benefit patients, as would home delivery of medication, which they explained was difficult due to NHS charges:

“At one point we had it set-up years ago where patients could get the drugs via the local pharmacies in community and the GPs would do it but then it got like, because it was cheaper and it would save the NHS VAT and things like that but then they started charging the hospital for a tariff that made it more expensive, so then we had to take it all back in-house.” (PR05)

Reflecting earlier comments about the structure and set up of outpatient care, the need for more practitioner time in clinics was expressed by PR02, PR04 and more support for patients by PR14:

“I think just some maybe some more identified support for those patients because they do need more than they’re getting really.” (PR14)

PR02 also felt that CML patients would be working more with primary care services and nurse-led clinics in the future:

“We’ve got so many long-term CML survivors and now stoppers, more of the support, monitoring is going to have to move into community type scenarios with our oversight or nurse-led scenarios.” (PR02)

Regarding organisational aspects of outpatient care, PR02 also suggested linking patients together for support and offering access to blood results to improve care:

“I wonder whether we could improve on linking patients to other patients or mentoring or CML mutual support.” (PR02)

Finally, when considering improvements to clinical practice, PR11 stressed the need for guidelines to support their nurse led CML phone clinic:

“You know this nurse led clinic, you know what to do with the patient in the clinic but I think if you would have some of those guidelines and pathways which we can follow it makes life easier for everyone, yeah.” (PR11)

6.1.4 Sub-theme 4: Practitioner perspectives on caring for CML patients

CML patients were generally seen by practitioners as comprising a small proportion of their workload, with most considered as having a stable disease with uncomplicated treatment and a good prognosis, particularly when compared to other haematological malignancies:

“CML would be less than 2 or 3% of my overall workload, for two reasons: one, it’s actually quite rare, you know, when you see the number of patients we have, things like myeloma and lymphoma and even acute leukaemia and certainly chronic lymphocytic leukaemia coming through the clinic, CML is a relatively rare disorder.” (PR06)

Some compared CML to other diseases and referred to its historic prognosis:

“It used to kill people about 20 years ago but now they live life like normal actually. I don’t think there are, I think they die of something else now rather than die of CML because the control is that good.” (PR15)

Few patients were said to be refractory to treatment, experience disease progression or need acute treatment, and the disease was perceived by several practitioners as more like a chronic disease than cancer:

“When you compare it with acute myeloid leukaemias or dysplastic syndrome then obviously CML patients have much more, better prognosis, it’s basically now chronic benign condition if I would say.” (PR11)

Several of the same practitioners also noted that this more straightforward pathway did not apply to all patients and some, such as those who had had a poor response to TKIs, went on to require stem cell transplant:

“She failed all of them and now she’s on ponatinib she’s for transplant even though she’s 70 plus because we’re quite far down the line.” (PR15)

Less frequently, practitioners explained how some CML patients require extra support in the remote monitoring clinic, despite being much less numerous than those with other diseases:

“We’ve got about 3,000 on the outreach services and only about 30 are CML patients but in relation to the other patients, we tend to spend quite a bit of time on them and that’s a lot to do with the prescriptions.” (PR03)

The general view of CML as “low key” was also suggested in the thematic synthesis.

6.1.5 Summary of theme 1

Most practitioners had a special interest or specialised in CML, and were experienced haematology consultants or CNSs. The cancer centre hospitals had specific CML clinics, as did some of the smaller local hospitals, suggesting that the volume of patients was not the only barrier to establishing clinics at such hospitals. There appeared to be three groups of MDT meetings which hospitals took part in, some working more independently than others. Practitioner’s general haematology caseload varied depending on whether they saw inpatients, as well as outpatients. Also, there were some differences in the general patient population of the hospital area from more elderly with increased co-morbidity, to younger people. Most clinicians working with primary care teams reported a positive experience.

Despite variations in characteristics and settings, practitioners agreed on many aspects of their decision making, including use of clinical guidelines and communication with colleagues. Decision making was related to treatment; treatment choice and management of response, toxicity and tolerance, and stopping TKIs. Practitioners valued sharing experiences and derived reassurance from working with colleagues when making complex decisions. Other influences included clinical assessment and the availability and profile of TKIs.

In terms of the set-up of outpatient follow up for patients with CML, HMDS was seen very positively, despite results being delayed at times. Several practitioners felt they had inadequate time with patients in outpatient clinics, with little time to discuss issues such as side-effects. CML dedicated

clinics offered continuity of care and a specialist service to patients, but could be difficult to balance with other clinical demands, and remote monitoring and hospital pharmacy services received mixed opinions. Forward planning of clinics and good clinical practice were reported to improve patient experiences, offering continuity of care, timely results and psychological support.

There was overlap between practitioner and patient interview data regarding hospital pharmacy delays, the benefits of remote monitoring, home delivery of medication, CML specific clinics, the efficiency of clinics and clinical expertise. Practitioners were able to provide their broader perspective of clinics, and areas relatively unknown to patients, for example HMDS services and the organisation of clinics. They also highlighted the need for more time to talk during appointments, as is reflected by the patients, many of whom placed great emphasis on the human aspects of their care, including the nature of staff, and the explanations and psychosocial support they provided. More forward planning was not suggested by practitioners as an improvement to care despite this being regarded by some as a positive aspect of their service.

Considering the variability within the region's CML care provision it is interesting that practitioners used similar methods to underpin medical decision making, through the use of international guidelines and communicating with colleagues, particularly via the MDT and clinical lead for CML. Most practitioners reported that CML patient care required less time than other haematological malignancies, with the suggestion that this was related to CML having a good prognosis and less complicated treatment, something also suggested in the thematic synthesis. Whilst some practitioners acknowledged that for some patients, the disease could progress and require more aggressive treatment, several perceived CML as a low level or chronic disease. Despite most interviewees having a particular interest in CML, and several running CML specific services, this appeared to be a common view. This, in addition to their focus on treatment when discussing clinical decisions, may lead us to believe the practitioners held a narrow, medical perspective on CML patient care. However, the following chapter explores the remaining interview data, which shows clear practitioner awareness that, from the patients' perspective and context, living with CML may be a much more complex experience.

Chapter 7 Findings: practitioner interviews 2

After establishing the broader context of their practice, this chapter examines the wider perspective of practitioners as they describe the impact of CML on patients, the influence of socioeconomic factors on management and outcome, and how they managed CML beyond the treatment decisions discussed in *theme 1*. Again, some findings from the patient interviews are referred to where appropriate, in order to present a deeper picture of patient care.

7.1 Theme 2: Impact of CML and its treatment

Theme 2 looks at practitioner data concerning the impact of CML and its treatment. The group described side-effects and the psychological and day to day impact for patients living with CML. In this theme we begin to see that in addition to their clinical view of CML, practitioners were aware of how patients' individual circumstances and context may interact and influence the impact of the disease and treatment.

7.1.1 Sub-theme 1: Side-effects

Some practitioners reported that TKI drugs were generally well tolerated by most people:

"If it looks like CML it probably is going to be CML, so I stick them on imatinib and get them back in a weeks' time after counselling them about it. They tend to tolerate that really well." (PR20)

"...generally, the TKIs are well tolerated." (PR01)

PR02 and PR06 reported that side-effects are usually worse at the beginning of treatment:

"Side-effects do settle down for the majority of people over the first few months. It's trying to help people through mostly the early stages I guess." (PR02)

However, most of the group, including most of those who felt that TKIs were generally well tolerated, also discussed the possibility of side-effects and there seemed some agreement that not all patients tolerate TKIs well, sometimes needing to switch treatment:

"I have had some patients where they've really struggled and because of side-effects we've switched treatment." (PR10)

The side-effects most commonly reported by practitioners were gastrointestinal (GI) problems and fatigue, which patient interviewees confirmed they frequently experienced. GI symptoms included nausea, sickness and diarrhoea (PR01, PR03, PR05, PR14, PR20) and were often linked to imatinib, possibly as it was the most commonly used, with diarrhoea often also related to bosutinib:

"We've just had a gentleman who's had awful gastro-intestinal upset on imatinib. We've stopped it, it goes away. We've changed him onto a different drug." (PR20)

"It's a really strong medication. They know they're taking it. They feel sick every day. They have diarrhoea every day...it's just, it's real." (PR14)

GI side-effects could influence adherence, which is discussed in more detail in later themes, and the patient interviews:

"I speak to her she's like, oh I don't always take it. I think she only takes it 3 times a week because of the nausea that it causes her." (PR03)

Fatigue was also described by practitioners, being worse at diagnosis and challenging to manage:

"The biggest thing these guys complain of is tiredness and tiredness is a nightmare, you've just had a bad nights' sleep but it's more than that in these guys." (PR20)

"...fatigue, I say we don't really handle very well in the out-patients department." (PR01)

The patient interviews confirmed fatigue as a common, often ongoing side-effect. Cardiovascular effects were discussed by practitioners, also reflecting the patient data. PR01 and PR06 reported such effects in the context of second generation TKIs, which influenced decisions about which medication to use:

"[We] put her on dasatinib and she's had a torrid time. She's been admitted with pleural effusion, she's got hypertension. I worry about pulmonary hypertension with her. So, she's stopped dasatinib and she's going to change to something else but we monitor the side-effects quite closely." (PR01)

Individual examples were given of periorbital oedema due to imatinib, along with skin rash, an allergy to nilotinib, mental health problems related to nilotinib and a case of liver failure in a patient taking imatinib (PR01, PR05, PR14, PR20):

“One of my patients was diagnosed in pregnancy about 23 weeks gestation when she was 23 years’ old, she delivered a nice health baby and then went into liver failure, probably mostly due to her imatinib but also because of the other drugs because she’d got a wound infection.” (PR20)

Interestingly, muscle pain was rarely described by practitioners, despite this being one of the most common side-effects reported by patients:

“...they [patients on treatment] also get some unexplained leg cramps and weaknesses and things, neurological type things.” (PR14)

Furthermore, respiratory side-effects discussed by some patients were not reported by the practitioners. A small number of practitioners referred to some TKI side-effects as low level, perhaps implying a comparison to diseases with more acute impacts, however, there seemed to be an understanding that the patient may not see it the same way:

“Some people do have on-going, what I would classify, mild symptoms. For the patient it may not be that mild but it’s not enough to stop treatment, so they’re happy to continue with their current treatment and manage the side-effects.” (PR10)

Some practitioners talked about the effects of stress and co-morbidity on side-effects, which begins to demonstrate practitioner’s awareness of each patient’s social context:

“Then patients are stressed, their head aches, can you blame them for medication, what sort of side-effects are coming from somewhere else and can then be, you know a link with the drug so then again.” (PR11)

PR14 and PR20 also suspected a relationship between gender and side-effects, both feeling that women had more side-effects. This was explained by women reporting more than men, or men having a higher threshold for side-effects:

“They [men] don’t tend to have quite as many side-effects as the female patients but me, being sexist and anecdotal but I think generally I think female patients are better at mentioning things. The blokes will just say, I’m a bloke I don’t get these side-effects.”
(PR20)

In line with patient data, practitioners also explained the challenge of caring for individuals with co-morbidities, some emphasising the difficulty in distinguishing TKI side-effects from other illnesses, and two considering those with co-morbidities more likely to struggle with side-effects:

“...the ones who do have some side-effects, it can sometimes be difficult to establish if it’s related to the drugs or if it’s other co-morbidities.” (PR10)

There was an agreement that co-morbidities, particularly along with older age, made choice of TKI more complex, as previously reported in *theme 1 (sub-theme 2: factors influencing clinical decisions)*. PR06 also pointed out that some patients with co-morbidity were able to tolerate TKIs and achieve good disease control:

“But they might be, you know, the most unfit, the most, you know, the person with multiple co-morbidities, you know, but as long as they take their imatinib they’re still quite likely to do well.” (PR06)

7.1.2 Sub-theme 2: Psychological impact of CML

Many practitioners spoke of the psychological impact of CML at diagnosis, which was reported by some to continue as patients lived with the disease over time. This, as we have seen, reflects patient accounts of their psychological reaction, in particular the shock they felt at diagnosis. Patients receiving a cancer/leukaemia diagnosis were often described by practitioners as being in shock, the diagnosis presenting a ‘challenge’, ‘burden’, and being ‘life-changing’. Despite advising that CML holds a good prognosis for most, some practitioners reported that the diagnosis may still be difficult to accept:

“A lot of people are very alarmed hearing the word leukaemia at diagnosis and as much as we then try and set that in context the majority of people with CML do very well and good response to drugs is compatible with a normal life span, it can take a while for that to sink in and quite a few results for the people for that to sink in. In the meantime, people can be very stressed.” (PR02)

These practitioners expressed an understanding that despite seeming a less complex disease to some, the individual patient may not view it that way:

“...as soon as she heard the word ‘cancer’, and this is about 8 years ago, has just been completely anxious and distressed and a real psychological mess really, bless her.” (PR04)

As patients start treatment and disease monitoring, practitioners described ongoing patient worry or anxiety, particularly around the time of their three-monthly blood test; again reflecting the patient interviews:

“...they do have that underline worry especially just when they’re coming for their 3-month appointment.” (PR10)

Living with a chronic cancer could be seen as challenging, and this may cause more anxiety than in patients with aggressive blood cancers:

“We know from things like work done in patients with follicular lymphoma that a watchful waiting or having something done that isn’t very intensive does cause more anxiety than more intensive type chemotherapy like RCHOP for high grade lymphoma or AML type therapy.” (PR20)

Others highlighted how the impact of CML varied, depending on the individual’s coping mechanisms:

“...in terms of how people actually cope with the news and to start taking the drugs, everybody is different and there’s not a clear cut [way].” (PR02)

Several practitioners said the psychological impact on younger people may be greater, with agreement that diagnosis can be a bigger shock and take longer to accept in people with much life ahead of them, and less experience of illness:

“Certainly, to begin with, you’re going to be, you have a chronic illness and you’re going to be taking the drugs for a long period of time is a real burden for some people particularly younger people who didn’t see this coming.” (PR02)

Some practitioners reported that younger people consequently needed more psychological input, such as that provided via their peers and a youth support worker at the Teenage and Young Adult service, run at one of the cancer centre hospitals. This perspective of the psychological impact on younger people is valuable, as all the patients interviewed in this study were aged thirty-eight or over at diagnosis.

7.1.3 Sub-theme 3: Day to day life

There were mixed reports from practitioners regarding the impact of CML on daily activities. Several practitioners described ways in which patients’ day to day lives could be affected by their disease and treatment, whereas there were also reports, often from the same practitioner, that patients should be able to continue a ‘normal life’:

“We’re promoting them to have as normal life as possible, and that’s what we expect them to have, a pretty normal life.” (PR02)

Perhaps, from the practitioner perspective, this impact was seen within the context of other haematological malignancies, as PR06 implied:

“Most of them are just doing well on oral therapy, so it doesn’t mess around with their lives in a way that something like intravenous chemotherapy would.” (PR06)

The main reports of daily life impacted were employment and travel. PR05 and PR06 explained that most patients could continue to work, whilst experiencing minor side-effects:

“Most of ours [patients] hold down jobs and whatever and are fine.” (PR05)

Despite this, some practitioners also explained that employment could be affected by fatigue and extra support could be required, specifically: a youth worker helping young adults and teenagers back into work or education, and a CNS who wrote supporting letters to employers, asking them to consider patients’ side-effects and promote flexible working:

“...if work need any, we’ll often do supporting letters for work to explain their needs and that, you know, work may need to take into account their side-effects, be a bit more flexible working.” (PR04)

PR06 and PR15 felt that holidays and travel shouldn’t be affected:

“Travelling, just need to bring the tablets because it’s not, it’s quite handy. It’s not like injections.” (PR15)

However, there could be difficulties obtaining travel insurance, with some practitioner accounts describing how they write supporting letters for insurance companies and customs, and share advice based on the experiences of other patients:

“...talking to patients in general you get a feel for who’s doing a good deal [in travel insurance] at the time and whatever, so you can post them in that direction.” (PR05)

PR10 discussed the effect of some TKIs on eating and nutrition, particularly nilotinib , and PR20 the impact treatment may have on socialising. PR14 also pointed out how obtaining life insurance and buying a house may be impacted:

“You have to be mindful and it will affect your life because you’ll have to say you’ve got leukaemia if you want to get travel insurance, if you want to buy a house, if you want to get life insurance.” (PR14)

Practitioners’ accounts of the impact on day to day life had some overlap with patient interviews, where problems with employment and travel were commonly reported. However, the effect on employment seemed more pronounced among patients, with several reducing working hours or leaving their jobs. Patients also reported many other issues affecting daily life, including mental wellbeing, sport, getting around, and how these interacted with co-morbidity and social issues.

7.1.4 Sub-theme 4: Patient perspective on life

Several practitioners shared their perception that CML patients held a positive perspective on life with their disease, following diagnosis:

"It's [TKI treatment] transformed their life hasn't it. It's enabled them to live really. Yeah they feel quite positive about things." (PR03)

Practitioners believed there were benefits to the acceptance of disease and adaptation to life with CML (PR02, PR14); and that this could lead to patients being able to cope better with their disease (PR08), adhere to their TKI medication, manage side-effects and even have better outcomes (PR02, PR10):

"I find with any disease if you have a positive attitude you usually have a better outcome and you're more likely to be compliant with medication and better at managing side-effects." (PR10)

PR11 added that it was often an absence of side-effects and a series of good blood results that provided this more positive outlook and improved coping:

"I think if the patient does not face any side-effects of the medication, and you are basically then start, you're starting to, giving them positive information, good results, then the patient copes much more, better." (PR11)

This idea of patients adapting to their disease and maintaining a positive perspective is mirrored in the patient data. However, patients also provided detail on the psychological process of adaptation and the struggle to remain positive, a concept noted by few practitioners who felt some (PR02) or most patients did not hold a positive outlook and may struggle (PR04):

"I think it's quite rare that people are positive about it really. I do find that people struggle living with long term chronic cancers." (PR04)

There were also differing opinions about the influence of patient perspective, with PR02 and PR06 agreeing that a positive outlook would not necessarily bring better outcomes:

"I think sometimes you get people who've got very positive attitudes who do very badly, they've just got the wrong disease and other people grumpy and negative and so on, and still be the archetypal creaking gate you know." (PR06)

"I don't think you have to have a positive attitude to get good results." (PR02)

Reversing the influence of outlook on coping and outcome, PR11 described a patient who changed drugs and achieved a better molecular response, but with no impact on quality of life:

“It actually made him molecular remission but it did not have any impact on his quality of life at all. He says ‘I am now in major molecular remission and what’s the difference now?’ I couldn’t have answered that.” (PR11)

7.1.5 Summary of theme 2

Theme 2 begins to show how, in addition to complex disease and treatment decisions, practitioners also had an awareness of the impact of CML and how this effected daily activities and the patient’s perspective. Most practitioners accepted that side-effects occurred, and those raised matched patient data, with the notable exception of muscle pain/cramp, which was rarely mentioned by practitioners but commonly reported by patients. Some practitioners discussed aspects of patients’ lives, which may modify side-effects, including stress and gender, and also the interaction with co-morbidity, demonstrating their ability to see CML across a larger cohort of their patients.

Many practitioners referred to the psychological impact of CML with shock at diagnosis and ongoing worry and anxiety, reflecting the patient data. Younger people were considered more vulnerable to psychological difficulties, again demonstrating the practitioner’s ability to view commonalities across their patients. Practitioners’ reports of the impact of CML on daily life, mainly referring to employment and travel, were more ambivalent, in contrast to patient accounts which suggested a more significant effect and several other factors not mentioned by practitioners. Patient outlook was generally reported to be positive, which some thought could help them cope with side-effects, adhere to medication and have better outcomes. These reports partly reflected patient perspectives, however patient data revealed a struggle and effort involved in retaining this positivity and anxieties they held regarding the future.

7.2 Theme 3: Wider influences on CML management

Theme three describes how practitioners saw the impact of various socioeconomic factors and highlights their awareness of the patient’s social context. Practitioners often considered the effects of socioeconomic situations on disease experience, outcome and/or management. This reflects earlier discussion regarding the impact of stress, gender and co-morbidity on side-effects and practitioners’ awareness of psychological and daily life changes due to CML (*theme 2: impact of CML and its treatment*).

Socioeconomic factors in general

The support of family, friends and others to enable patients to cope with their disease was frequently referred to by the patient group, and played an important part in their experience. However, few practitioners referred to this:

“I think patient who are from a stable family, have good background, good support, definitely cope much better than the patient who do not have this support.” (PR11)

Some practitioners reported that lifestyle factors, such as smoking and drinking, could be related to self-management and/or outcome. PR04 suggested that those with lower socioeconomic status may be less likely to choose a healthier lifestyle:

“The lower socioeconomic groups perhaps don’t pay attention to their health before this diagnosis, generally not compliant with dentists, GPs, in general and I’m not saying they’re the only group that do use alcohol and smoking but they maybe factors.” (PR04)

While PR01 felt that education may impact on outcome, other examples were given of patients with problematic backgrounds and good disease response; hence poor outcomes were considered bad luck:

“I can equally think of examples of people who’ve come from extraordinarily difficult backgrounds, asylum seekers, people who have been suicidal, people who have been in really difficult scenarios and they’ve taken the tablets successfully and done very well.” (PR02)

Two areas suggested as possibly linking socioeconomic factors and outcome were medication adherence and co-morbidity.

Socioeconomic influence on adherence

The narrative literature review presented significant evidence to suggest that adherence to treatment is related to disease response, and many practitioners spoke of a possible relationship between socioeconomic factors and adherence. It is important to note here, that during these discussions, practitioners often referred to examples of patients, or their general experience or ideas, so were generally speculating on this link, rather expressing a firm belief:

“If [the] patient has a difficult social background, and lots of other issues and problems in their life then obviously, it’s my feeling or the way how I see it, they are more likely to forget the medication because they are obviously having lots of other issues and problems.” (PR11)

The socioeconomic factor most frequently discussed alongside adherence was education, with poorer understanding of treatment and disease considered to underpin lack of adherence (PR03, PR04, PR05 and PR19), although this relationship may not always be clear cut:

“I suppose the less educated you are, the less you understand why you’re doing what you’re doing and everything but then by the same token a lot of those patients will be like, ‘my doctor has told me to do it, so I’m gonna do it and I don’t necessarily understand why I’m doing it but he’s told me I’ve got to do it’. So, in some respects they actually tend to be quite adherent because they wouldn’t dare do anything else. Whereas a lot of people, that you know, Google everything, know everything, are like, ‘I know better than you. I don’t need it.’” (PR19)

Practitioners also suggested a link between mental health problems or learning disability, and poorer adherence:

“Anyone with mental health issues and their compliance is not going to work, there are the patients that don’t do well. Their disease goes out of control.” (PR20)

PR14 suggested that young males may be more likely to adhere if they are in a stable relationship:

“He only became adherent when he was in a solid relationship with a partner.” (PR14)

The support of family in promoting adherence was reflected in patient interviews, although more detail was provided about the roles relatives undertook. Differences in spoken language may also contribute to poorer adherence:

“Language barriers are a barrier; language difficulties are a barrier to compliance” (PR04)

Finally, homelessness was also mentioned:

“One has, one young one has problems with, she’s homeless and then doesn’t come to clinics and doesn’t take medication.” (PR15)

PR10 noted though that without observing the patient’s whole life it is very difficult to know about their background, or how they self-manage their CML:

“You have to be a little mouse in their daily life.” (PR10)

Co-morbidity and socioeconomic factors, adherence and tolerance

The possible relationship between co-morbidity, socioeconomic factors, and disease management and outcome is perhaps more complex. As discussed in *theme 2 (sub-theme 1 side-effects)*, co-morbidities could restrict treatment choice and make this more challenging; it could also be related to poorer tolerance of TKIs. This struggle was described by some practitioners and as PR06 explained, could lead to gaps in treatment, thereby affecting response:

“...and they may end up moving from one drug to another and not get a continuity of treatment of people who perhaps are more motivated, have got less co-morbidity are able to better tolerate the treatment.” (PR06)

It was suggested that those in poorer socioeconomic groups may have more co-morbidity:

“But then people with lower socioeconomic groups probably do have more co-morbidity, don’t they?” (PR06)

7.2.1 Summary of theme 3

Theme three demonstrates the understanding practitioners had of the socioeconomic context of patients’ lives, and how it may impact on their disease management and outcome. This is demonstrated by the theme at the end of the top line of figure 15, showing the breadth of practitioner awareness. The understanding practitioners had of this area has been highlighted previously in *theme 2 (impact of CML and its treatment)*.

Suggested socioeconomic factors influencing disease outcome and self-management included family support, lifestyle factors and a poorer background. Conversely, some practitioners described patients with difficult socioeconomic situations who managed well and had good outcomes, and those with good circumstances and poor outcome, possibly due to bad luck. Although there was

evidence of practitioner awareness of the importance of family support, it did not reflect the emphasis patient interviewees placed on their networks, in helping them cope with their disease, which could lead to better outcomes.

Adherence, as we have learnt, is strongly linked to disease response and it was commonly reported that poorer socioeconomic factors could relate to worse adherence, for reasons such as lack of disease understanding, or other social problems being prioritised over disease management. The link between co-morbidity and socioeconomic factors is more complex perhaps, with the suggestion that people with a poorer socioeconomic background were more likely to have increased co-morbidity, and that such co-morbidity was related to poorer TKI tolerance, which could lead to more breaks in treatment and poorer adherence, ultimately affecting treatment responses.

Themes one to three have demonstrated that the practitioner group held broad perspectives on patients with CML; from their own medical view to an awareness of the impact on patients' lives and their social context. The final theme reveals if this awareness is applied to practice, and if contextual factors are modifiable, in the long term care of CML. It explores how practitioners described aspects of managing patients with CML beyond clinical decision making described in *theme 1 (sub-theme 2: factors influencing clinical decisions)*.

7.3 Theme 4: Management of CML and its treatment

Theme 4 encompasses the topics practitioners discussed regarding the management of patients with CML beyond treatment decisions. This included adherence and management of side-effects, as well as advice provided at diagnosis and over time.

7.3.1 Sub-theme 1: Adherence

Several practitioners pointed out that most patients adhered well to TKIs and suggested that only a minority had difficulty. This was echoed in the patient interviews, although most of the group had missed medication at some point:

"I think most people are sufficiently worried about their disease, so they will stick to take the medication." (PR10)

Some practitioners spoke about patients who had deteriorated due to non-adherence, leading to progression to blast phase and sometimes the need for stem cell transplant:

“All the way through, we’ve had every single line of treatment going and we, we’re at a point now where it’s now getting into blast crisis and there’s not a lot we can do because he won’t...he’s kind of his own person.” (PR19)

However, such cases seemed rare:

“We’ve had two patients now in the past 5 years’, because of refusal to take their therapy for one reason or not, have progressive disease that we can do nothing about, both of whom did respond to a TKI or could have had a transplant, but they would not have complied with the therapy.” (PR20)

Intentional non-adherence

Most practitioners described their experiences of intentional non-adherence, the main reasons being patients deciding they didn’t want to take TKIs, or because they had side-effects. Several reported patients who did not want, or did not like, taking medication; did not feel they needed it, or did not follow advice to take it. This topic was not seen in the patient interviews:

“...it’s just they decided they don’t need it, they don’t want to take their medication. Difficult.” (PR04)

When described specifically, practitioners defined such patients as being unaccepting or ‘in denial’ about their disease:

““No problem’, ‘I don’t have a problem’, you know, ‘I don’t have that problem. So putting your head in the sand sort of like not wanting to own up to the fact that you’ve got a condition.” (PR01)

Some mentioned patient complacency or failure to take responsibility for managing treatment:

“They need to take a bit more responsibility with regards to the prescriptions, you know, rather than letting it all run down.” (PR03)

Patients were sometimes described as ‘disappearing’ from clinic follow up, meaning they were not receiving prescriptions and their disease status was unknown:

*"I've had a couple like that who haven't... and they disappear off the radar but then when they come back poorly because they haven't done it, it's like, well we told you."
(PR05)*

Several practitioners suggested that a decision not to take medication could be influenced by alcohol/drug use, younger age and mental health issues. Taking recreational drugs or alcohol and the social life often associated with this, could be incompatible with TKI side-effects, yet seen as more important than adherence:

*"I don't want to get a GI upset, I'm not taking my imatinib this weekend'. I've got a couple of young lads that are cocaine people, they don't like taking it with their cocaine."
(PR01)*

Younger patients were seen by some as more likely to choose not to adhere, as they may feel 'invincible' (PR15). Young men in particular were reported as more likely to not 'be bothered' about adherence (PR14), and young women were said to worry about the impact TKIs on their appearance:

"If they come and they've got no periorbital oedema...I just think, yeah you're not taking it, the young girls especially because they just say, 'I don't like the way it makes me look...ALL [acute lymphoblastic leukaemia - arising from CML progression] won't look good either, but there you go.'" (PR14)

Experiences were described by practitioners of patients who, due to mental health or psychological issues, were of the opinion that they would sooner end their life than take their medication:

*"I think in the end she just decided that she didn't want to take any medication, she thought, you know, she'd rather die. It was just all very sort of unnecessary."
(PR04)*

TKI side-effects were described by several practitioners as a further cause of intentional non-adherence, which reflected the patient interviews. This was reported by practitioners to impact on holidays and their social activities:

"Sometimes they'll [patient's will] say, 'oh I'm going on holiday and they [the tablets] make me feel a bit urgh, so I'm not going to bother for two weeks.'" (PR19)

Situations were sometimes described by practitioners where TKIs were not taken due to symptoms attributed to this medication, including abdominal pain and palpitations, but actually these symptoms related to another morbidity:

“We had one guy who had decided that he was having palpitations or something and it was his medication, so he kept stopping it and then he’d start it again and he kept doing it on and off at home and just letting us know that he’d done it and that. In the end we said, you need to go to A&E, there’s clearly something wrong if you’re having palpitations and he’s been diagnosed with some kind of heart issue now and we kept saying to him, this is not your medication.” (PR19)

Intentional non-adherence could also result from medical advice to stop TKIs, again mirroring patient findings. Some practitioners highlighted that this advice may arise due to kidney problems, chest pain, for reproductive purposes, or due to incompatibility with treatment for other conditions:

“I can’t remember what contraindications are but he was almost sort of hospitalised with his ulcerative colitis, couldn’t go to work and the MAB [monoclonal antibody therapy] he was having had just changed his life and we had to stop it for a bit.” (PR14)

PR05 practitioner reported a patient stopping TKIs due to attempting to conceive, but not under medical advice:

“He was adamant that he did not want to be on his Glivec even though he’d been on it for ages while they were trying for a baby and he stopped it and when he came back to clinic 3 month later, I had to tell him to go back on it because his PCR within a 3-month period had shot up.” (PR05)

Unintentional non-adherence

Most practitioners noted unintentional non-adherence, with some saying patients may simply forget to take their tablets, including those self-managing via the remote monitoring service, where patients take responsibility for ordering their own prescriptions:

“Not all of them, but when they come away from the clinic setting, then they either forget or they don’t think it’s important till they get down to their last few tablets.” (PR03)

Forgetting to take medication was the most common reason for non-adherence cited by the patients interviewed; who also discussed triggers such as a change to routine. Socioeconomic factors were again discussed by practitioners in terms of unintentional non-adherence, echoing *theme 3 (wider influences on CML management)*. Several interviewees believed people were more likely to forget their medication if they were managing other difficult issues in their lives; for example, problems with housing or finances:

“My understanding would be that if [a] patient has a difficult social background, and lots of other issues and problems in their life then obviously, it’s my feeling or the way how I see it, they are more likely to forget the medication.” (PR11)

Examples were also provided of those with learning disability and mental health issues, and people whose first language was not English having less understanding of their disease, which affected adherence:

“Maybe they just don’t really, despite the best attempts of explanation, understand the information. Maybe they have issues around reading or learning disabilities, so there is a group who may not comply with their treatment.” (PR06)

Finally, practitioners described people who had issues with awareness or acceptance of their disease, and lacked organisation or self-management skills. Patients may also miscount medications, not plan ahead or struggle to comprehend instructions. Again, these topics were not reported in the patient interviews, highlighting the benefit of the interviewing practitioners:

“Maybe it’s just their comprehension of needing to take the drugs as well and understanding that somebody’s comprehension is a bit, different.” (PR04)

Identifying non-adherence

Practitioners discussed how they identified non-adherence. This included: dialogue with patients, investigative tests, prescriptions and symptoms. Patient dialogue, i.e. asking a patient directly, or the patient telling the practitioner themselves, was the most common method.

Dialogue with patients

Asking patients about their adherence was often triggered by deteriorating BCR-ABL results, or a lack of demand for prescriptions.

"I think it doesn't cross their mind that it's just being honest that they still have tablets, 'you're not taking your tablets'... 'you shouldn't have enough', 'oh yeah I miss a few here and there'." (PR15)

Talking to patients about adherence was sometimes a routine question in clinic, whereas PR11 experienced difficulty approaching this question, due to potentially sensitive reactions from patients:

"I generally do ask. I generally, I would say that is one of my standard questions: 'are you taking the tablets?'" (PR10)

"In fact, it's hard to ask these patients about, you know, the compliance because obviously some can take it quite personally." (PR11)

PR08 emphasised the importance of making patients feel comfortable and able to talk about adherence, and PR01 expressed concern about those on the remote monitoring scheme:

"So, I'd like to think that those patients on the remote PCR testing are adherent, but because you're not seeing them and you're not, asking them, I don't know, I don't know. It's just making it more remote isn't it." (PR01)

Several practitioners said patients themselves may tell them that they have missed or stopped taking their medication, usually temporarily:

"Sometimes people will just volunteer: 'I've run out, I didn't bother getting in touch with anybody' or 'I didn't like the side-effects, so I stopped.'" (PR02)

Non-reporting of non-adherence

There were also reports from practitioners about patients who do not talk to them about non-adherence. This was also seen in the patient interviews, with several reporting they had not informed their practitioner of such events. PR10 described research showing that practitioners underestimate patient adherence to TKIs. Reasons given by patients for non-reporting included its infrequent occurrence, it not causing them to become unwell, or that they did not want to bother the doctor. A few practitioners spoke in stronger terms about patient non-reporting of non-adherence, describing some as 'lying' to them:

"We look at the PCR and like I'd like to think that my patients didn't lie to me, but they do, you know." (PR01)

PR14 considered younger men and women less likely to inform them about non-adherence, with PR05 including those with an older diagnosis. Both practitioners implied they were required to be suspicious of non-adherence:

"I hate being suspicious because that's not in my nature but I always am because I think, 'you're not taking it'. I think you have to be realistic about challenging early and being a bit, just say, 'Your bloods don't look like you're doing what you should be doing, do you want to talk about it?'" (PR14)

Patients could avoid discussing non-adherence by not attending follow up appointments:

The problem is if they're not taking it regularly, and you know they[re] not because... they don't turn up to the clinic appointment and they're not ringing a week later saying, 'I'm really sorry I forgot, I've run out of tablets.'" (PR01)

Investigative tests

Test results were frequently used to identify non-adherence, most commonly BCR-ABL levels, which was described as improving or deteriorating and could prompt questioning about adherence:

"From molecular [unclear] BCR-ABL transcript, if we [see] some increase then we question that, and [if] there was an issue with medication, if it was delivered on time, if the patient is OK [and] they did not forget to take the medication." (PR11)

BCR-ABL using graphs routinely produced by HMDS could be used to help monitor adherence:

"...if you see somebody bobbing about on the graph, then that's the reason to intervene." (PR01)

Deranged full blood counts, and particularly raised white cell counts, were also described as indicative of non-adherence, prompting questions and dialogue with patients, in addition to bone marrow testing to measure cytogenetic response to medication:

"...if they [patients] come and they look absolutely fine and their bloods are all over the place, you've got to be suspicious really." (PR14)

The reliability of BCR-ABL levels as an indicator of non-adherence was questioned by some practitioners who pointed out that although BCR-ABL graphs could appear to show a good response, patients may still be non-adherent; also, deteriorating BCR-ABL may be due to a mutation, rather than non-adherence:

"I had one guy that I thought was totally non-compliant and it turned out that he was but he had a mutation." (PR01)

This is of interest as some of the patient group reported that missing an occasional dose had not affected their disease or molecular response, suggesting this method may not reliably identify non-adherence.

Other methods

Non-adherence was also identified through patients having not collected enough prescriptions, or having an excess of medication:

"I have one lady who I'll say; 'right you need a prescription'. 'No [she replies], I've got plenty'. So, she obviously isn't taking [her medication] regularly." (PR05)

In PR02's hospital, pharmacy would inform practitioners of uncollected prescriptions:

"...sometimes pharmacy can alert us they can't have taken their full amount of medication because some of it is still sat in pharmacy waiting collection." (PR02)

This monitoring was not reported among patients interviewees, suggesting they may be unaware of this method of identifying non-adherence. Finally, symptoms could be used as indicators of non-adherence, including an enlarged spleen and jaundice:

"If they have an abnormal blood count and then you examine them and they've got an enlarged spleen as well, then you know something's not wrong and then you do a bone marrow and you would really grill them about, are you sure you're taking your medication, type thing." (PR05)

Of interest here is that patients often reported no symptoms (or consequences) following missed doses.

7.3.2 Sub-theme 2: Managing non-adherence

Most practitioners described their approach to patients thought to be non-adherent; the types of advice they gave; and the methods used to optimise adherence. Some also discussed what they felt motivated patients to adhere.

Approach to discussions about non-adherence

Being supportive was described by practitioners as the importance of making patients feel comfortable, which was in line with patient interview findings describing their appreciation of psychosocial support:

“I guess it would be trying to, I don’t want to say scare them, but obviously if the result deteriorates that would be a big scare for patients and then kind of try and work, try and see what we can do to help them to take the medication.” (PR10)

Several practitioners spoke about the value in exploring why the patient was non-adherent, and understanding the challenges they may face:

“It’s exploring why. It’s all about the why’s, whether it’s a practical issue, whether it’s a side-effect issue, whether it’s a psychological issue and it’s very different in different circumstances.” (PR02)

Maintaining a patient-centred approach and persevering with discussions was highlighted by practitioners, as well as the importance of improving patient understanding of treatment. However, it was also reported that inadequate time was available to spend with patients for such purposes. Several also spoke of being honest and taking a challenging approach when discussing non-adherence. This included showing deterioration in BCR-ABL graphs, being upfront with patients, questioning non-adherence when it was first suspected, and the use of strong directive language:

“Well, we tell them. We show them the BCR-ABL graphs going into red zone.” (PR15)

“I say: ‘Do you want to die? Don’t be so stupid, just take your tablets, it’s only 1 or 2 a day. Stop it. Just go and do it.’ (PR05)

It is important to note that some practitioners used a combination of supportive/challenging techniques when discussing adherence with patients, although PR20 felt each practitioner had an individual approach:

"I think that comes down to each individual clinician, how they interact with their patients. You can shout and scream and wiggle your finger at them, but it's not necessarily going to make them take their tablets." (PR20)

Patient advice on adherence

Several practitioners advised patients at diagnosis that they needed to adhere to their TKIs and to report back if they couldn't take them:

"But when somebody's first diagnosed now, we've got a drill and we quote the 'David Marin' study and just say: 'if you miss 3 in a month this will affect your PCR and this could affect your outcome, so tell us if you're not taking your medication.'" (PR01)

Although there appeared to be some implicit understanding of the importance of adherence in the patient interviews, they did not reveal any explicit discussions about it, so this practitioner data adds to our understanding. Some practitioners said they encouraged patients to inform them about the impact of side-effects on adherence, and reassured them that if they initially adhered carefully and had a good response, they could perhaps stop TKIs in future:

"...just to make sure that they actually understand what they're taking, and why they're taking it and that. If they're not managing their side-effects, you know, if there are side-effects and it's really making them not want to take them, then they need to let us know about it, so we can maybe help, and sort that out." (PR19)

Patients could be provided with advice about medication timing and the use of normal routines as a prompt. This reflects the most common adherence strategy used by the patient group:

"With certain drugs like nilotinib, it's quite difficult to take certain hours, you know, around eating and they often need quite a lot of support working out when the best times are going to be to take that." (PR04)

However, PR20 encouraged patients to take their TKI, even if they had missed the optimum drug timing:

“Everybody says: ‘Oh, but [the] box says I’ve got to take this with food, with that, at this time of day, on an empty stomach, and have an empty stomach for another 4 hours. I say: ‘Okay, if you leave the tablets in the box, it ain’t going to work. If you take that tablet at any time with any food or drink, I don’t care. You will have a better response if it’s in you, than [if] it is in the box.’” (PR20)

Despite emphasising the importance of discussing non-adherence with patients, some practitioners were unsure if missing doses had a significant impact:

“If you look at how stable the patients are and how [the] vast majority are in molecular remission, well if they occasionally forget the drug, what impact does that actually have? I don’t think anybody really knows.” (PR10)

Others felt that missing an occasional dose (sometimes with the proviso that the patient must be in a stable MMR), would not have a serious effect:

“Life, and work and study. I get around that by reassuring people that they can miss some of their tablets. I try and persuade them to take tablets ninety percent of the time, so they can miss one weekend a month.” (PR20)

This view was shared by several of the interviewed patients who reported a belief that missing an occasional dose was not concerning. Furthermore, when patients explained the advice given by practitioners after missing a dose, this varied from general information, to specific instructions on what to do next.

Other methods to optimise adherence

Some of the group described a process of repeatedly contacting patients who had not attended follow up clinic, so had not received a new prescription. These reports again provide insight into a concern not raised by the sample of patients interviewed:

“We do send them a clinic appointment. They don’t come, then we continue to send them clinic appointments, because it’s a very easy treatable disease.” (PR15)

Patients with more complex adherence needs were sometimes referred to colleagues in psychology:

“People know the outcomes can be fatal but that still doesn’t necessarily translate into being able to get regularly on treatment, and then we do have obviously psychologist support locally.” (PR02)

Involving family members in adherence management was also discussed. PR15 was unsure if this had any effect in young adults, but PR14 and PR20 reported that younger men tended to adhere better when in a stable relationship, or due to a change in circumstances:

“His wife got pregnant with their second son, and us and her gave him a good stern talking to and suddenly on the same drug he’s gone into major molecular response and has been brilliant ever since. But without that trigger his life would have been fairly chaotic.” (PR20)

In contrast, several patient interviewees cited family as an important support for their adherence, usually helping them to remember to take TKIs, but also obtaining prescriptions and medication devices. Finally, some practitioners talked about how CNS and consultant roles varied in managing adherence. PR02, a CNS, tended to refer patients to consultants if they wanted to temporarily stop their TKIs, whilst PR01 (CNS), PR04 (CNS) and PR06 (Consultant) suggested adherence management was the role of the CNS:

AH: “What kind of problems would the doctors end up asking for you to come in on?”

PR04: “Usually if they’re suspecting compliance issues.”

Interestingly, the practitioner group did not mention the use of medication devices such as pill boxes or alarms, which were discussed by several of the patient group.

Adherence motivation

Some interviewees discussed what they felt motivated patients to adhere to TKIs, which included fear:

“He is adherent, he does take his medication because he’s scared stiff that anything is, anything is going to happen to him.” (PR01)

PR03 explained one patient’s motivation was their trust in the service and PR05’s understanding was that people had a certain personality type making them more likely to adhere:

“I think some people, and you see it with everything, some people will take their medication religiously, as they are told, as it says on the box, and will do exactly as they’re told. Other people just think they know better, but that’s patients in general.”
(PR05)

7.3.3 Sub-theme 3: Managing side-effects

Earlier in *theme 2 (sub-theme 1 side-effects)* practitioners acknowledged the likelihood of side-effects: commonly GI symptoms and fatigue. Some went on to discuss how these were dealt with, which often involved medical management but also the provision of advice and collaborative working with GPs. Some practitioners, however, discussed a lack of patient-reported side-effects.

Medical management of side-effects

Several practitioners described switching TKIs in patients experiencing difficult side-effects, including GI side-effects (imatinib) and pulmonary hypertension (dasatinib) (PR14, PR01). However, PR06 pointed out that there could be problems with most TKIs:

“These drugs do have side-effects and if you’re convinced that: a) it’s due to the drug; and b) the side-effects are severe, you probably move them onto something else, dasatinib, bosutinib or ponatinib, there’s lots of choice, although they all have their own problems.” (PR06)

Other medication was sometimes reported as prescribed to control side-effects, in particular GI symptoms:

“Antiemetics for nausea...and a lot of them are taking loperamide daily or alternate days, or whatever they get into a habit of doing.” (PR14)

PR20 also explained that for some, reducing TKI dose would be considered:

“If we can’t get a full dose into you, take it every other day or let’s give you half a dose and see if that will make you take it’... and you adapt what you’re doing based on what they say or do.” (PR20)

PR01 felt some side-effects weren’t managed well by practitioners, particularly fatigue and GI symptoms:

“Fatigue, I say we don’t really handle very well in the out-patients department. Whether it’s chicken and egg, whether patients present with CML and are fatigued or the medication is making them fatigued or it’s a combination of both, we don’t really deal with that very well in our clinic.” (PR01)

Advice on managing side-effects

Several practitioners provided advice to patients at diagnosis about treating side-effects:

“I try and go over the fact that you will get some side-effects and you will have some toxicity and this is what we do to manage it, so that they’re armed really.” (PR14)

Some spoke about supportive discussions with patients, encouraging them to talk or phone if required, and helping them understand treatment and why side-effects occur:

“I think in trying to encourage people to stay on therapy who do have side-effects it’s trying to help them see the positives and the reasoning behind it all and why the side-effects are happening... knowledge is helpful isn’t it.” (PR02)

This contrasts with some of the patient reports, which implied a lack of understanding of possible side-effects, and descriptions of practitioner difficulty or their own reluctance to talk about this in clinic. Finally, practitioners also provided advice on lifestyle, including the timing of nilotinib so it is taken on an empty stomach, taking TKI medication at night to avoid GI side-effects, and remaining fit and active:

“...not a lot of them get nauseous with it and if they do, we just tell them to take tablets at night before they go to bed, instead of taking them in the morning” (PR05)

Working with GPs to manage symptoms

Previously in *theme 1 (sub-theme 1 practitioner experience, role, practice and clinics)* several practitioners discussed working collaboratively with GPs, often to manage the risk of cardiovascular side-effects:

“But we do pick up on this more now [cardiovascular side-effects] and if we have patients with this and they have had a high blood pressure, we tell the GP to manage them a bit better.” (PR15)

PR05 added that GPs may be contacted regarding other co-morbidities, such as depression and along with PR19, cases where the patient was directed to their GP or A&E as their symptoms were felt unrelated to CML medication:

“...they go: ‘Well my GP gave me that’, or they go: ‘Yeah I’ve got this symptom.’ [I ask] Have you been to your GP?” [Patient says:] ‘Yeah they gave me that [medication] but I’ve read the side-effects and I don’t want to take it’. [I think:] ‘Well go back to your GP, you know.’” (PR05)

Some of the patient group also reported on their GP care, with positive comments about their reliability, listening skills and the provision of extra care due to their CML.

Patient strategies and co-morbidity

PR14 commented that those with a longstanding diagnosis were more likely to self-manage symptoms, with PR01 providing an example of a patient who found a way to manage GI side-effects:

“He [patient] has rice with his bosutinib, and the starch from rice limits his diarrhoea and he’s found now, because that drink Dioralyte that you get when you’ve got diarrhoea, that’s got rice starch in it, so he’s done a bit of working on it and he figured out that if he takes rice with it...so, any patient that comes along, we say, you know, just try a bit of starch when you’re taking it.” (PR01)

In contrast, the patient data suggested that several used self-management techniques, including over the counter remedies, muscle stretching for cramps and by ‘*learning to cope*’.

We saw in *theme 2 (sub-theme 1 side-effects)* that several practitioners were concerned about distinguishing side-effects from co-morbidities. This concurs with patient interviews, often among more elderly patients:

“Older patients are more challenging in that they don’t tolerate the medicines very well and if you look at the patients that we take back to the MDT for poor response, it’s usually the older patients because they’re having side-effects or they’ve got the co-morbidities.” (PR20)

Patient motivation to report side-effects

Many practitioners discussed the reasons patients may not always report side-effects to practitioners. This awareness is supported by patient interview data showing several were reluctant, hesitant or had difficulty discussing side-effects. Muscle cramps were frequently experienced by patients and often dealt with independently; but were not highlighted as a common symptom by the practitioner group (*theme 2, sub-theme 1 side-effects*). There was also some lack of patient awareness about TKI side-effects. Some practitioners felt under-reporting was due to patients not wanting to bother their doctor, which was related to busy clinics and doctors having limited time. This reflects practitioner reports of pressure on clinic time in *theme1 (sub-theme 3 set up of outpatient care)*. At one hospital, this led patients to talk about side-effects with CNSs rather than doctors:

“Like I said, we have only twenty minutes in the clinic, it’s twenty-minute slots and they are problem focussing on, just to get, for them the most important information, and then right yeah, I think sometimes the patients have question for you and then for [CNS], so they are completely different, yeah (laughs).” (PR11)

To counter limited time in clinic, PR20 suggested practitioners needed to create time for patients to discuss such issues:

“You don’t always give them the time they need. If you invest in that time and say, ‘ok, what’s going on? What do you need?’ They will tell you. You can figure out a more sensible treatment plan and sometimes we’re not very good at that as a profession because we think, oh we’re in a rush to get to the end of clinic.” (PR20)

Some practitioners thought that patient reluctance to inform them about side-effects was due to perceptions that these were low level and could be self-managed, reflecting some patient accounts that they had ‘learned to cope’:

"...[patient mentions] 'diarrhoea... I'll make sure I don't go too far from a toilet'. Well actually, if you'd told us that we'd do something about it." (PR20)

"If they're ticking along okay, all be it having those low-level side-effects, they never pick up the phone and ring us. We never actively seek them out, because they think they're okay." (PR01)

An additional reason for hesitancy in discussing symptoms highlighted in the patient interviews, was reluctance to take extra medication, something not mentioned by practitioners. Also, some patients reported difficulty discussing side-effects due to their co-morbidities, feeling the practitioner *"did not respond"* or being fearful of the practitioners' response. Finally, as referred to in *theme 2 (sub-theme 1 side-effects)*, PR20 suggested that there may be gender differences in reporting side-effects:

"I think female patients are better at mentioning things. The blokes will just say, I'm a bloke I don't get these side-effects." (PR20)

7.3.4 Sub-theme 4: Advice at diagnosis

Practitioners discussed advice given to patients at diagnosis, in addition to that previously described on managing adherence (*sub-theme 2 managing non-adherence*) and side-effects (*sub-theme 3 managing side-effects*). PR02 and PR19 described taking an encouraging approach at diagnosis to support patients to feel they could discuss any problems with them:

"You can't read their minds and you don't know what's concerning them, so upfront it's my biggest take home message is, to tell us how they're feeling medically and how they're feeling psychologically." (PR02)

Information

Part of the practitioner group referred to the provision of standard information at diagnosis. Some reported offering explanations about CML and its treatment, the clinical team and how to contact them, and details of outside support, including a local cancer support centre, patient support groups and welfare advice:

"I think standard across the board [are] information about the disease, where to contact our nurses, patient support groups." (PR15)

Practitioners said they provided written information, although PR20 warned that this may not be helpful to patients with lower literacy:

“The literature that comes out of the drug companies is lovely if you are a medic or a nurse that can read it and understand what it’s talking about, but some of the patient stuff is just, they’re going to look at it and chuck it in the bin and say, that doesn’t make sense.” (PR20)

In the patient interviews, several appreciated the written literature they were given, which helped to explain the disease and treatment and was useful for family and friends. An information source not evident in practitioners’ accounts was advice found on the internet, which was used by a number of the patient group. Several practitioners implied that the information needs of patients were greater at diagnosis than later in the disease trajectory, with patients having more questions and/or consultations initially, and PR05 described the provision of extra appointments for patients struggling to absorb information at diagnosis:

“If we’ve got a patient who, we think they don’t quite get it or whatever, then we will book a formal session with the chemo nurses for them to go through things in a bit more detail, if we think, nah, they don’t really have a clue about what they’re telling them.” (PR05)

“I tend to see them quite a bit first off, to make sure they understand their tablets.” (PR14)

Prognosis and reassurance

Many practitioners reported reassuring patients at diagnosis that they could or should continue to lead a normal life, that the disease was treatable and that their life expectancy remained normal:

“A lot of people are very alarmed hearing the word leukaemia at diagnosis and as much as we then try and set that in context the majority of people with CML do very well and good response to drugs is compatible with a normal life span.” (PR02)

“We do encourage them [patients] to lead as normal life as possible.” (PR04)

A few emphasised the long-term nature of CML or compared it to other chronic illnesses:

“I tell patients, this is like hypertension now, we can control it very well and if we control it well, there’s nothing much to worry about.” (PR15)

This reflects several patient accounts describing the value of psychosocial care, and particularly the reassurance and explanations of prognosis, provided by practitioners. However, patients expressed mixed knowledge of their disease process and prognosis, with some significant misunderstandings. Some practitioners pointed out the success of new treatments in recent years, which was an area of little knowledge in some patient interviews:

“We’ve got different options and it used to be transplant, interferon, hydroxycarbamide, those were your options. Then it was imatinib or transplant and the other stuff. Now you’ve got imatinib, nilotinib, dasatinib and something else, transplant, all the other things and suddenly you’ve got loads more options.” (PR20)

The view of CML as a low level disease, in terms of its successful treatment and chronic nature was noted earlier (*theme 1 sub-theme 4 practitioner perspectives on caring for CML patients*). Most practitioners viewed it as a stable, uncomplicated disease, with well tolerated treatment, meaning it would have little impact on day to day activities. However, many also spoke of the psychological consequences of CML, its impact on daily activities, and range of side-effects. Some reflected on this mixed perspective, cautioning that an optimistic outlook of CML as a treatable chronic disease should be balanced with advice about the risk of not treating the disease:

“I try not to sort of say, ‘ah if you’re going to get a leukaemia this is the one to get’, because I think they need a sense of we are only where we are because the drugs are as good as they are, but if you and we don’t do what we should do, you’ll be in exactly the same position as somebody 20 years ago would be.” (PR14)

Stopping TKIs

Advice about possibly stopping TKIs in the future was mentioned earlier, in relation to encouraging adherence (*sub-theme 2 managing non-adherence*), and some practitioners reported advising patients at diagnosis that this could occur:

“Perhaps after a few years, maybe even sooner, you can actually come off the drug.” (PR06)

PR01 and PR02 noted how advice has changed due to findings from ‘Stopping Study’ trials:

“You used to say, life-long medication, but in view of the ‘Stopping Studies’ and the way it’s going to go with the new guidelines, because they’re stopping things in the new guidelines...you can say, well actually at some point you’re may be able to come off your therapy and 50% of patients stay off their therapy. So, the focus is changing now.”
(PR01)

There was, however, mixed understanding of the possibility of stopping among some of the patient group, with no evidence this was related to time since diagnosis.

7.3.5 Sub-theme 5: Ongoing advice

As described in the previous sub-theme, several practitioners said that as patients progressed through treatment, and their disease became more stable, their information needs reduced:

“Patients are sort of freaked out by the amount of information we give them at the beginning and then slowly come back to it and then the second or third visit they’ll come in and say, ‘oh we’ve finally got around to reading this book and we’ve read all about imatinib, why did you put me on that and not one of the other ones?’ And over time that changes and they become CML experts often as well.” (PR20)

At this point, patients may prefer to use their time with practitioners for occasional support or reassurance about their health, or for a broader chat, as suggested by PR11 and PR19. Several patient interviewees expressed their appreciation of this psychosocial support, particularly if they were familiar with their practitioner:

“They chat completely about something else, about their holiday and grandkids, yeah (laughs) so they are just basically coming for the results, and [to] get another prescription for TKIs” (PR11)

Despite reports of information needs declining over time, practitioners (including some of those cited above) described how some people had ongoing difficulties. Patient interview data supports this, with several reporting anxiety about the future, disease progression and premature death.

“There’s always the anxiety every time they come to clinic about their blood results. I get lots of phone calls for blood results, you know, I may not see this patient in clinic but they’ll ring me a couple of weeks later to find out what their CML, BCR-ABL bloods are and I know there’s probably about 8 to 10 patients that do that after every clinic. So, it does raise a lot of anxiety.” (PR04)

PR14 described how practitioners may also have ongoing involvement in managing co-morbidities:

“I also try and get them to include me in anything else that they’re having done. So, we’ve got a lady who’s got amyloid. We’ve got a young lad who’s having some problems with sort of an urticaria rash periodically and stuff and in order to get them sorted we try and get them to keep in touch with us really. So, we get involved in all sorts of things really.” (PR14)

The main information described as being relayed to patients after diagnosis appeared to be molecular monitoring results, provided in a coloured graph by HMDS indicating response in terms of their BCR-ABL level. Some practitioners said patients varied in their desire to see the graph, with some benefitting from this information, and others being reluctant to see it, preferring the practitioner to tell them the result. As discussed, many of patient group were aware of response measurement, with several referring to the HMDS results graph:

“Some people are quite happy to let the BCR-ABL ratio rest with us, you know, they’re not too bothered to know what it is, whereas other people it’s a wasted clinic visit unless they know.” (PR06)

7.3.6 Sub-theme 6: Practitioner anxiety and CML management

There were practitioner accounts which described feeling anxious about some patients, including those with side-effects or adherence issues. Words used included ‘challenging’, ‘worry’, ‘difficult’ and ‘upset’. PR20 and PR01 described examples of patients with serious, difficult to manage side-effects:

“I worry about pulmonary hypertension with her. So, she’s stopped dasatinib and she’s going to change to something else, but we monitor the side-effects quite closely.” (PR01)

Anxiety regarding non-adherent patients who had disease progression requiring stem cell transplant, or who had died, was expressed:

"...he [patient] was very challenging. He was very challenging, but I do have a real soft spot for him still and I still speak to his mum even now. She rings me a couple of times a year but he was just a troubled soul unfortunately." (PR14)

PR04 and PR05 described managing their own feelings at such times, by recognising that patients are responsible themselves for their adherence to medication, and may have had other difficulties, as well as CML (PR14):

"I think you don't get blasé or complacent the longer you do this job, but you do get an understanding of that at the end of the day, and you stop getting so upset when people aren't doing what you tell them to do, you start to think well actually they have the capacity to make a decision. They are grown-ups. They are adults, you've done your job." (PR05)

"He was just a troubled soul unfortunately and he even said one day, 'I'm not going to make old bones, so don't waste your time', and he wouldn't have done, without CML, he wouldn't have done." (PR14)

7.3.7 Summary of theme 4

Theme 4 described issues in the management of CML beyond those relating to treatment decisions, as detailed in *theme 1 (sub-theme 2 factors influencing clinical decisions)*, predominantly including the management of TKI adherence and side-effects. Many practitioners agreed that most people adhered well, and they reported similar reasons for unintentional and intentional non-adherence. They also demonstrated awareness of the importance of social context in understanding adherence. A further two reasons for non-adherence were described that were not seen in the patient interviews; unintentional - due to lack of awareness or organisation skills; and intentional – due to patients simply not wanting to take their medication.

The most commonly described method of identifying non-adherence was BCR-ABL results; the reliability of which was questioned by some, which mirrors the patient interviews. An excess of prescriptions was also an indicator of non-adherence, something patients appeared unaware of. Dialogue between patients and practitioners often explored how non-adherence was identified through questioning or could be patient-initiated. There was concern from some practitioners of

patient non-reporting of non-adherence, particularly among younger people or those with less recent diagnosis, with some practitioners describing this in strong terms, such as “lying”.

Practitioners described taking a supportive stance to discussions about managing adherence, or sometimes, if needed, a more challenging approach, with advice focusing on the timing of medication and use of reminders. Whilst some gave strong advice to adhere, others said it was reasonable to miss an odd dose. Practitioners also expressed their own uncertainty about the significance of infrequent non-adherence, a difficulty they shared with patients interviewed. Sometimes psychology services or family support were used to promote adherence, although the latter was more strongly emphasised in the patient group. Other techniques for supporting adherence, mentioned by patients but not practitioners, included the use of medicine devices and also polypharmacy. Some practitioners felt that fear of disease progression or personality type might motivate patients to adhere.

When managing side-effects, practitioners often took a medical approach, although some offered more general, supportive advice around medication regimes. Some encouraged patients to understand their treatment better, explored side-effects and suggested more time should be committed to this in clinic. This contrasted, however, with several patient accounts of a lack of knowledge about side-effects and reluctance, hesitancy or difficulty discussing such issues in clinic. The challenge of managing side-effects alongside co-morbidity was acknowledged by practitioners and mentioned by patients.

In addition to managing adherence and side-effects, practitioners discussed more general advice. This often involved reassuring patients at diagnosis that their disease was treatable; that they could lead a normal life; and that they should anticipate an average life expectancy, and such reassurance was highly valued by many of the interviewed patients. Practitioners said they provided standard information (oral and written) at diagnosis; but did not mention the internet although several patients cited using this resource. Some staff maintained that patient need for information generally decreased over time, with some patients simply requiring reassurance at follow up. Often information was provided about molecular response, via graphs from HMDS, which were considered informative and useful by practitioners and patients. The need for information was thought to vary by level of anxiety or other psychological issues, which was in keeping with the patient interviews. Some practitioners described feeling anxious themselves about delivering care to patients with difficult side-effects or progressive disease due to non-adherence, despite understanding that adherence was largely the patients' responsibility.

7.4 Chapter summary (practitioner findings 1+2)

Thematic analysis of practitioner characteristics and settings demonstrated a broad range of experiences and backgrounds. Despite this, many agreed about the factors influencing their treatment related decisions, including the use of clinical guidelines and the value of support from colleagues. Some aspects of outpatient care were seen as broadly positive, such as the regional diagnostic laboratory (HMDS) and the forward planning of some clinics, whilst others received mixed reports including CML dedicated clinics and hospital pharmacy services. Several practitioners agreed that, during appointments, there was often insufficient time to discuss issues important to patients including side-effects. Many of the patient group agreed with this and placed great emphasis on the human aspects of care, such as staff responsiveness and the provision of psychosocial support. Practitioners also suggested that remote monitoring, nurse led telephone clinics and the home delivery of medications improved care, in agreement with some patient interviewees. Further forward planning was not suggested as an area for improvement, despite this being regarded positively by some.

Most practitioners reported that CML patient care required proportionately less time than for those with other haematological malignancies, with the suggestion that this was underpinned by CML having a good prognosis and simpler treatment. In addition to clinical decisions focusing largely on treatment, this may suggest practitioners held a purely medical perspective regarding care. However, later themes demonstrated awareness of the patients' wider context and the influence of this on adherence and side effect management.

Theme 2 showed similarities between practitioner accounts of the impact of CML and those of patients, but not in all areas. Most practitioners discussed potential side-effects, which accorded with those reported by patients, apart from muscle pain commonly reported by patients, but not practitioners. Reports of the psychological impact of CML were equally well reflected in both groups, however, changes in daily activities seemed more prominent and broader within patient accounts. Practitioners' perspectives, across larger cohorts of patients, were evident in their discussion of wider contextual influences on side-effects and psychological difficulties, such as age and gender. It was agreed that most patients held a positive perspective, which practitioners considered may help them adapt to their disease, however, patient accounts revealed that maintaining such positivity was more of a struggle than practitioners may have realised.

Theme 3 discussed practitioner reflections on patients' social circumstances and how these may affect their experience, ability to self-manage and disease outcomes. Of those issues discussed, the influence of social support seemed to be underplayed by practitioners compared to patients. It was

thought by some that poorer adherence may be linked to social circumstances, with poorer treatment understanding or stressful life events taking priority over adherence. In addition, a complex relationship between socioeconomic factors and co-morbidity was suggested as having a link with disease management and outcome. This theme confirmed that practitioners had a broad awareness of patients' social context, despite some factors being seen as outside their control. Further, some practitioners pointed out that poor outcome may be down to 'bad luck', as seemingly socially disadvantaged patients may also have good experiences and outcomes.

Earlier, practitioners described CML as a low-level disease with a chronic course that could be successfully treated. Patients were frequently considered stable and able to tolerate TKIs. Patients too, often explained that they had adapted to their disease and could live a 'normal life'. *Theme 4* demonstrates the extent to which practitioner awareness of the broader impact of CML, including the patient's context, was incorporated into their management, against this background concept of CML as a low level disease. It describes how practitioners managed CML beyond treatment decisions, and how their focus may be similar, or different, to that of patients. There seemed to be an understanding of patient need for reassurance at diagnosis and beyond, which is reflected in the patient interviews. Non-adherence was often identified through practitioner-patient dialogue and supportive approaches were frequently employed in discussions about adherence or side-effects, with practitioners identifying that more time was required for such discussions. This need for extra clinic time reflects earlier findings about practitioner understanding of the psychological impact of CML and the value patients placed on having supportive interactions with them. However the role of social support, particularly in managing adherence, as emphasised in the patient interviews, was not as strong in practitioner accounts; and although practitioners reported discussing side-effects, patient knowledge of these could be lacking. Furthermore, whilst practitioners reflected patient accounts regarding their reasons for hesitancy in reporting side-effects, they did not seem to be fully aware why some patients described having difficulty when they did enter these discussions. Practitioners also seemed to underestimate the use of medicine devices and polypharmacy to support adherence; and use of the internet by patients to research side-effects. Interestingly, practitioners shared differing opinions and uncertainties over the significance of missing occasional TKI doses, which perhaps explains why some patients were also confused.

Theme 4 also demonstrates practitioners' descriptions of patient accounts outside those interviewed in this study. In particular, they were able to describe types of unintentional and intentional non-adherence not seen in the patient interviews. Further, they commented on factors which may exacerbate non-adherence such as younger age and mental health problems. This reflects the benefit of their broad perspective across a wide cohort of patients. Finally, some practitioners

revealed anxiety over those who struggle with side-effects or experience disease progression due to non-adherence.

Overall practitioners demonstrated a wide perspective on patient experiences of CML, understanding social influences and psychosocial issues, as well as the complexity of co-morbidity. There were some areas where practitioners showed less awareness however, including the frequent occurrence of muscle cramps; the impact on work and other daily activities; the importance of social support; and the psychological struggle to maintain a positive perspective. Practitioners described under-reporting of non-adherence and side-effects, despite efforts to provide advice and information. This was reflected in the desire for more time to discuss such issues in clinic; and perhaps the demands of making complex treatment decisions and judgments on disease monitoring during appointments. The next chapter compares findings from patient and practitioner interviews in more detail, and relates this analysis to the thematic synthesis and wider literature, focussing on how patient and practitioner experiences influence the management.

Chapter 8 Contextual Summary: a comparison of thesis findings and the wider literature

This thesis has achieved its aims in describing both the patient and practitioner experience of living with and managing CML. It supports existing research and has produced some unique insights, which further develop this field. The findings especially support other qualitative research into CML in terms of emphasising the significant impact of the disease on patients' lives. However, the thesis also adds original findings to our understanding, such as the considerable impact CML and its treatment may have on employment and the high value patients placed on the support of family, friends and others in managing their experience. New findings were seen in the practitioner interviews and although some factors influencing patient experiences seemed to be underestimated, the interview material largely demonstrated a broad practitioner awareness of the socioeconomic context of patients' lives.

Practitioners also revealed characteristics of some patients they considered less adherent to medication, details not seen before in CML research. Importantly, this thesis adds evidence to support the concerning under-reporting, and difficulty reporting, non-adherence and symptoms, and contributed details of why patients chose not to reveal their concerns. The lack of a standard approach to practitioner management of non-adherence and an uncertainty over the significance of missed doses by patients and practitioners was revealed, a finding only previously reported in one non-UK study. Furthermore, interview analysis suggested disease concerns and anxieties were experienced by patients despite their outward presentation of a positive attitude toward their life with the disease, implying these concerns may not be expressed in medical appointments. Through the qualitative analysis and comparison to other literature, I was able to conjecture that this under-reporting may be related to the status CML holds within the context of a hospital environment; as a stable, well controlled and low-grade disease. I suggest a shared care model, in an environment more relevant to the patients' context may shift this perspective and enable communication and thus appropriate care for any disease concerns.

The summary and discussion chapters will consider major findings from this thesis in order to answer the main research aims; to explore and examine the experience of living with chronic myeloid leukaemia and the management of treatment and care. Findings from the patient and practitioner interviews will be compared in order to build a triangulated account of the patient experience and care provided. They will be contextually considered alongside the thematic synthesis and literature review, and with wider literature as appropriate. The contextual summary chapter (chapter 8) first explores the impact of CML, how patients and practitioners experience the disease

and its management, and how this experience, and their perceptions, may relate to the management of adherence and side-effects; and the discussion (chapter 9) sets CML within the wider context of chronic cancer and survivorship initiatives, and suggests how care may be altered to improve the patient experience.

8.1 Summary of key findings

Prevailing themes from both the patient and practitioner interviews in this thesis, demonstrate aspects of the experience of living with, and managing CML beyond adherence to TKIs, where much previous research is focussed. The impact of CML appears significant amongst patients, with side-effects, psychological consequences and changes to daily activities experienced by most. These may be modified by co-morbidity and socioeconomic circumstances. The impact of CML may be buffered by social support, the nature of hospital care and individual patient knowledge. Practitioners showed a broad awareness of several aspects of this experience, however much discussion regarding practice concentrated on the complexity of treatment decisions and less on managing such experiences. Patients described upholding a positive outlook on life but their discourse revealed the effort and sometimes struggle involved with maintaining this attitude, which perhaps was not revealed to their practitioners. This could be explained by practitioners viewing CML as a disease that is less complex, with a better prognosis than most, which was a message patients found greatly reassuring at diagnosis. However, this message could reinforce the idea in patients that the disease is less complicated, therefore should be manageable by themselves. This was further evidenced by the widespread use of patient led adherence strategies, the self-management of side-effects, the under-reporting of, and difficulty reporting, non-adherence and side-effects, and a lack of consensus from both patients and practitioners on the impact of missing an occasional dose. The difficulty with the notion of CML as a less complex disease is its chronicity, meaning patients live with its day-to-day effects for the rest of their lives, making its cumulative impact comparable to more acute disease with intensive, but short term treatment.

8.2 The impact of CML

The effects of living with CML and its treatment were wide-ranging, impacting day to day life and bringing psychological consequences. The majority of patients described the effects of their disease or treatment, a distinction (side-effects or disease symptoms) that was not always clearly described, with gastro-intestinal problems (GI) and muscle cramps or pain being the most frequent, followed by fatigue. These findings are supported in the thematic synthesis, which noted that GI issues, fatigue and pain were common. These three symptoms are also reported as significant in the wider

quantitative CML literature (Zulbaran-Rojas et al., 2018; Efficace et al., 2014^c, 2013; Williams et al., 2013; Efficace et al., 2012^b). Interestingly, whilst the practitioner interviews acknowledged GI symptoms and fatigue, they rarely mentioned muscle cramp or pain as side-effects. Mismatch of patient and practitioner perspectives about symptom burden is confirmed in other related literature, with patients rating some symptoms (e.g. trouble concentrating, drowsiness and skin problems) more relevant to health-related quality of life (HRQOL) than their practitioner (Efficace et al 2012^b). Furthermore, physician underestimation of overall symptom severity, fatigue and muscle cramps/pain was more marked than estimation of GI symptom severity, and did not vary by physician characteristics (e.g. experience, number of patients seen, and duration of patient/physician contact) (Efficace et al 2014^c). Jiang, Yu and Gale (2018) examined broader TKI related concerns of CML patients and haematologists, reporting that patients were more concerned about the adverse effects of treatment than their haematologists.

The experience of diagnosis and living with CML also impacted on patients' psychological state, with many describing shock at diagnosis, ongoing worry over possible progression and general health anxieties. Again, these findings were echoed in the thematic synthesis but were not as prominent in the quantitative literature. Efficace et al (2011) compared their cohort of CML patients to a matched control group from the general public, finding no significant difference in mental component scores in their HRQOL measure. Using the same measure and sampling, another study concurred (Phillips et al., 2013), but found significantly increased levels of depression and anxiety using different measures. Perhaps this highlights the difficulties capturing psychological effects with quantitative tools. Despite noting the good prognosis associated with CML, several practitioners expressed an understanding of patient distress at diagnosis and the mental challenges of living with CML over time. This was reflected by Efficace et al (2012^b), who also reported patient and practitioner worries and uncertainties about the future; but unexpectedly (compared to previous studies) also found HCP over-estimates of psychosocial symptoms. Patients interviewed for this thesis also described how having CML impacted on day-to-day activities. This thesis highlighted the influence of CML on working lives, which was not a strong theme in the thematic synthesis or reports from practitioner interviews. Several patients either reduced hours or stopped work due to the disease, a finding supported by CML patient surveys, which reported the significant impact of fatigue on ability to work (Zulbaran-Rojas et al., 2018; Efficace et al., 2013). Practitioners also seemed to under estimate the importance of generally 'getting out and about', taking holidays and being able to continue hobbies, as often discussed by individuals in the patient group.

The modifying effect of co-morbidity on patient experience was raised in patient and practitioner interviews, with several patients reporting co-morbidity interacting with symptoms and causing

changes to day to day activities. Practitioners also discussed the complexities of co-morbidity, how these exacerbated side-effects, and the challenges of distinguishing side-effects from co-morbidities, particularly when considering treatment decisions. Difficulty surrounding practitioner management of co-morbidity was not seen as a theme in other qualitative work included in the thematic synthesis. Furthermore, practitioners showed an awareness of socioeconomic influences on CML patient experiences, identifying factors such as lifestyle, poorer background and lack of family support, as well as the complex relationship between side-effects, co-morbidity and adherence. This broad perspective was not reported by Wu et al (2015), in the only other qualitative study interviewing practitioners.

The impact on patients of side-effects, psychological symptoms and day-to-day activities is reflected in the body of work on HRQOL and symptom burden in CML throughout the last decade, as noted in previous paragraphs. Following the widespread use of imatinib since 2000 and its consequent unparalleled improvement in survival, issues regarding ongoing side-effects and quality of life now occur in a life-long context, so are more prominent and important to researchers (Baccarani, Efficace and Rosti, 2014; Efficace et al., 2011). As referenced earlier, case-control studies in Italy and the USA reported CML patients having significantly worse physical HRQOL compared to controls, which was more pronounced in younger age groups (Efficace et al., 2011). These included “clinically meaningful” levels of fatigue and depression, worse physical HRQOL, anxiety, and overall symptom burden (Phillips et al., 2013).

8.2.1 Assessment of symptom burden and quality of life in CML

The effects of TKI treatments have commonly been measured using the National Cancer Institute Common Criteria for Adverse Events (CTCAE), a system for classifying oncology treatment effects and severity, routinely used in clinical practice and clinical research studies (National Cancer Institute 2017). This supports clinical decision making and is included in UK, European and American guidance on CML treatment decisions (Smith et al., 2020; Radich et al., 2018; Steegmann et al., 2016). Whilst the intention of this measure is to identify and avoid the harmful effects of high-grade treatment (Efficace and Cannella, 2016; Flynn and Atallah, 2016), it is typically completed by practitioners, with recent ELN guidance observing that in CML trials TKI side-effects have not been patient reported (Hochhaus et al., 2020). Baccarani, Efficace and Rosti (2014) argue that few adverse events, such as pain, can be measured empirically in this way. This is compounded by research findings showing practitioner tendency to underestimate symptom severity (Efficace et al 2014^c). Furthermore, when reviewing side-effects using the CTCAE reported by major CML drug trials, authors note a wide

variation in the reported frequency of side-effects (Efficace and Cannella, 2016; Baccarani, Efficace and Rosti, 2014).

The first TKI, imatinib, was shown to significantly improve quality of life compared to its predecessor interferon, and side-effects are commonly described by clinical trials as low grade for TKIs under the CTCAE system (Efficace and Cannella, 2016). However, authors researching the burden and impact of CML on HRQOL agree that even these low grade side-effects can represent a large burden for patients and may significantly impair quality of life as patients potentially endure them over a lifetime (Efficace and Cannella, 2016; Flynn and Atallah, 2016; Baccarani, Efficace and Rosti, 2014). In response to this, two Patient Reported Outcome (PRO) measures were developed; the MD Anderson Symptom Inventory CML module (MDASI-CML) (Williams et al., 2013) and the European Organisation for Research and Treatment of Cancer HRQOL CML module (EORTC QLQ-CML24) (Efficace et al 2014^b), both of which comprise a main survey with additional CML-specific questions. It is argued that such self-completed tools more accurately measure treatment effects than practitioner estimates (Efficace and Cannella., 2016). The MDASI-CML (26 items: 19 core, 7 CML specific) was developed and used to measure the symptom burden of 152 CML patients over a year (Williams et al 2013), finding a third had high symptom severity throughout the follow up period. The EORTC QLQ-CML24 supplements the established EORTC QLQ-C30 with 24 CML items, including a measure of symptom burden (Efficace et al., 2014^b). Both tools were developed using systematic methods to a high standard (Baccarani, Efficace and Rosti, 2014) and their use is suggested to support clinical decision making, research and other areas of care (Efficace et al., 2014^b; Williams et al., 2013). However, neither practitioners nor patients interviewed for this thesis mentioned the use of any questionnaire or PRO measure, raising the issue of whether such tools are used in general clinical practice. The underestimation of muscle cramp/pain, and the impact of CML on employment by practitioners highlights the value of such tools in more accurately assessing the patient experience of CML.

8.3 Buffers on the impact of CML

8.3.1 Social support

The importance of support from family, friends and others in dealing with the impact of CML was discussed by all patients. Despite there being some reference to social support in the practitioner interviews, it received much less emphasis, and also seemed less prominent in the thematic synthesis. In a qualitative study examining the experiences and needs of patients with a different haematological malignancy, non-Hodgkin's lymphoma, who had received chemotherapy, a

significant theme was the “need to feel supported throughout the cancer experience” (Swash, Hulbert-Williams and Bramwell, 2018). Family support was particularly appreciated, with patients noting the impact of any lack of this support (Swash, Hulbert-Williams and Bramwell, 2018). Literature concerning social support is greater in chronic disease which, as discussed later, has similarities with CML in its requirement for lifelong management. Whitehead et al (2018) found similar notions pertaining to family support, addressing emotional and practical roles, advocacy, support for patient self-management, and details on how families carried out these roles. A review by Dwarswaard et al (2016) argued that patients cannot manage their disease alone and require support not just from practitioners but also other patients and family, emphasising that relational support was a critical factor in this. It is worth pointing out that in this thesis, several patients also discussed valuable support from their employers, as well as other support including online communities and MacMillan cancer centres. In the practitioner interviews, peer support arose only in terms of a service for teenagers and young adults set up at one of the hospitals. The importance of support from others with chronic illnesses was also highlighted by Dwarswaard et al (2016).

Interestingly, Swash, Hulbert-Williams and Bramwell (2018) found non-Hodgkin lymphoma patients had difficulty accessing peer support services as they did not typically define themselves as having ‘cancer’, but rather ‘lymphoma’. Overall, it appears from the findings of this thesis and further literature, that social support is vital and performs various functions in supporting patients to cope with, and manage their disease. Finally, the findings of this thesis support theory from psychology in that the quality of relationships and how a patient perceives them, for example having others to confide in and to share emotions, is an important element in the person’s ability to cope in addition to objectively measurable features of social support, such as the presence and size of a social network (Abraham et al., 2008; Sarason et al., 1987). Although both the MDASI and EORTC QLQ-CML24 have items relating to social support (for example: the question: “has your physical condition or medical treatment interfered with your family life?” in the EORTC QLQ-C30), the quality of this support perhaps needs to be assessed via open dialogue with individual patients.

8.3.2 Hospital system

Findings from this thesis describe patient satisfaction and also concerns about the organisation and management of their care. This perspective was enhanced by the practitioner data, which provides a much broader perspective of the CML service. It is important to note at this point that most patients were positive about their overall hospital care. Some difficulties, however, were noted. For example, although several patients commented on the efficiency of outpatient clinics, some also felt clinics were inefficient, particularly relating to long waiting times; and while some praised the

medication home delivery service, many had concerns over pharmacy provision, including sufficiency of stocks and delays waiting for medication. Practitioners shared some of these concerns and added detail to the landscape of CML care, by emphasising the benefits of running CML specific clinics, forward planning of clinics and raising concerns about the waiting area for CML patients, mixed with those waiting who had more acute disease. As a result of expert consultation discussed in the methodology chapter, feedback was received from a CML patient from a local haematology support group (see section 4.7.2, figure 13). Whilst the patient's response corresponded with many of the analytical themes, such as the experience of common side-effects, the value of family support, and missing an odd dose of medication due to a change in routine, the most salient feedback appeared to be around issues with the hospital system. A change in the hospital pharmacy system had caused a reduction in the supply of medicines issued, the stopping of home delivery and use of drugs close to their expiry date. Added to this were problems with delayed hospital letters since the use of a private mail company meaning "events could overtake letters", and a historical lack of consistency in the practitioner seen in clinic. Despite reporting overall care and treatment as "good/excellent", the patient described such issues as the "main side effect" of the disease. This provides a reminder that the impact of issues which may seem peripheral to disease management, can in reality can add unnecessary stress to a disease which, as we have seen in this thesis, already has a significant impact.

The CML patient-practitioner perspective on hospital care was described in the thematic synthesis, namely improvements suggested by study participants and qualitative authors, including improving practitioner advice, and changes to facilities and the cost of care. However, this thesis offered insights from both patients and practitioners by exploring outpatient care in more detail. Furthermore, literature exploring unmet needs in haematological malignancies reported little about outpatient services, other than some concerns over hospital parking (Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013). An area of work reflecting some of the findings from this thesis is that published by Harley et al (2012, 2019) and Boele et al (2019) exploring the unmet needs of patients with chronic cancer, a concept that is important in the context of CML and discussed later in this chapter. Harley et al (2012) conducted qualitative interviews with patients with solid cancers and their informal carers, describing a similar theme of "clinical services", which included difficulty with outpatient appointments, including lengthy waiting times. These findings were used to develop the Chronic Cancer Experiences Questionnaire (CCEQ) in which 28% of the items related to hospital outpatient experiences (Harley et al., 2019), with preliminary results indicating that although many were satisfied with their appointments, finding them reassuring, several were unhappy with waiting times (Boele et al., 2019). Such issues are not included in the MDASI or EORTC QLQ-CML24, although

it would seem sensible to conclude that the quality of hospital care may buffer the impact of CML, an example being that a full prescription of medication, supplied on time, could decrease the risk of non-adherence. Consequently, the CCEQ may be an appropriate measure to assess hospital care in the CML population.

8.3.3 Relationship with practitioner

The practitioner's nature/personality and the relationship they had with individual patients was a strong theme in patient interviews, supported by findings from the thematic synthesis. Patients placed great value on their practitioner being helpful, trustworthy, reassuring and interested in them as an individual. There was less data regarding this in the practitioner interviews, however several emphasised the limited time available to spend with patients during clinic appointments, suggesting they appreciated the worth of this relationship. Patients particularly valued reassurance from their practitioner, especially at diagnosis. The importance of reassurance was also highlighted by chronic cancer patients interviewed by Harley et al (2012) and those responding to the CCEQ in Boele et al's (2019) study. Such reassurance was important in the context of fear of cancer recurrence, which has been identified as the most common and frequently unmet psychological need in patients with haematological and other malignancies (Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013; Harrison et al., 2009), with a national survey reporting almost half of patients being fearful of recurrence up to 5 years post diagnosis (Department of Health, 2012). Although CML differs slightly from these other haematological malignancies as it does not follow a relapsing-remitting pathway, my findings indicate that the need for reassurance is still present, often stemming from a fear of worsening disease, which practitioners could reduce/alleviate with adequate reassurance. Although little literature exists on the relationship between CML patients and practitioners, one survey found that 41% of patients wanted to discuss "discomfort, anxiety and fear of the future" with practitioners, but were unable to do so, which the authors suggest was due to these concerns not being routinely discussed at outpatient appointments (Breccia et al 2015). In response to unmet needs identified in their 2009 review, Hall et al (2014) psychometrically tested the cancer specific Survivor Unmet Needs Survey (SUNS), which included several items evaluating emotional health (e.g. anxiety, loss of control and hope), and recommended this as an alternative tool for assessing unmet needs in patients with haematological malignancies.

Further evidence for the importance of the strong patient-practitioner relationship is provided by studies examining other haematological malignancies. As discussed earlier, a major need was to feel supported by people in their lives, including their practitioner with good patient centred communication seen as crucial, alongside frequent contact and information tailored to individuals

(Swash, Hulbert-Williams and Bramwell, 2018). Chronic lymphocytic lymphoma (CLL) has some similarities to CML in that patients may follow an indolent course over several years. Qualitative interviews with CLL patients on “watch and wait”, where patients are observed in clinic by their hospital practitioner and only treated when required, found that CLL was perceived as an “invisible condition”, with patients reporting that their practitioner lacked interest or did not understand how the disease impacted on them (Evans, Ziebland and Pettitt, 2012). It is unclear from this thesis if patients felt able to discuss anxieties with their practitioners, however it was clear that many appreciated reassurance and some revealed a psychological struggle to maintain a positive outlook, suggesting they harboured anxiety and fear. Patients also indicated difficulty communicating with practitioners regarding side-effects, a theme also discussed in more detail later.

8.4 Patient knowledge and awareness

There were areas of good awareness in the patient sample around how TKIs worked and disease response, however elsewhere this was mixed, particularly regarding the effects of treatment, prognosis and stopping TKIs, with some significant misunderstandings. Of particular concern is the lack of understanding of TKI side-effects. This was reflected in patient accounts of their practitioners’ explanations which, despite being praised in terms of explaining prognosis, disease and treatment, were said to be lacking when it came to side-effects. The thematic synthesis findings supported this, also finding information was lacking on drug taking routines and side-effects. This contrasts with practitioner reports that information was provided regarding the disease, treatment, adherence, side-effects and stopping TKIs. Interestingly, a literature review examining patient centred communication in haematology patient care, found that information on treatment side-effects was not well communicated by practitioners, which could impact on treatment decisions (LeBlanc et al., 2019). A strong finding from the National Cancer Survivorship Survey was that preparation for treatment by practitioners had a significant impact on the patient experience. This is further evidenced in the cancer literature (Moghaddam et al., 2016; Harrison et al., 2009) and in qualitative work relating to support for the self-management of chronic disease (Dwarswaard et al., 2016).

Two papers reviewed in the thematic synthesis found CML patients felt they needed little information at diagnosis and more as they adapted and learned to live with the disease (Graffigna et al., 2017; Guilhot et al., 2103). One qualitative study (included in the thematic synthesis) reported that patients wanted honest information, provided at the right time, on hospital visit frequency, social support and sexuality, in a form which was simple to understand, without medical terminology (Boons et al., 2018). In this thesis, although standard information was reportedly given at diagnosis, the provision of information after this period seemed less comprehensive and mainly concerned

with disease response, perhaps due to practitioners believing that information needs reduced over time. Reviews of unmet needs in patients with haematological malignancies indicated that outstanding information requirements were prominent (Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013). Of particular concern in patients with CLL and non-Hodgkins lymphoma, was limited awareness of the signs of progressive disease, which could lead to feelings of anxiety (Evans, Ziebland and Pettitt, 2012); and more broadly, that information was not 'tailored' to individuals needs and that prognosis and treatment discussions were inadequate (Le Blanc et al., 2019).

8.5 Summary: CML impact and its external and internal buffers

In summary, this thesis has highlighted the significant impact of CML, confirming the findings of existing qualitative and quantitative work. It also demonstrated that certain elements of this impact, may be over or under estimated by practitioners, and that some of these findings appear novel, not having previously been reported in the CML qualitative literature. Using a CML specific HRQOL questionnaire survey may correct any mismatch between patient and practitioner estimates of symptom burden and quality of life, however it is not clear if such a survey was used by the hospitals included in this thesis. I have suggested that various factors buffer the impact of CML, including social support, as evidenced in other haematological/cancer literature, but not prominent in qualitative CML studies as yet. Of further importance was the value patients placed on such support in this thesis. Although the two HRQOL surveys included items on this, the quality of social support and its value to individuals may need to be assessed directly by the practitioner in clinic. Hospital care, and patient satisfaction with its various components, was also found to be a possible influence the impact of CML, as emphasised by later patient feedback. However, this was not corroborated in the thematic synthesis, and indeed, there is little existing work on haematological cancers. Furthermore, these elements are not measured within the two CML HRQOL measures, although the CCEQ includes several items relating to hospital care and may be an appropriate tool in which to measure patient need.

Patient's relationships with their practitioners was highly valued, particularly with respect to the reassurance practitioners could offer. This was reflected in CML literature and wider work, and reflects a common fear of disease recurrence or progression expressed across cancer patients, indicating the potentially buffering effect of practitioners' reassurance in response to this. One way of measuring such concerns in the future, would be use of the SUNS tool, which includes items on fear and anxiety. Finally, patient knowledge and awareness, linked to the information they receive, can also buffer the impact of CML. An important finding from the patient interviews was a lack of understanding of TKI side-effects, which is supported by other literature. Practitioners interviewed

for this thesis seemed less aware of this, also believing information needs reduced over time, contradicting work in the thematic synthesis, which suggests patients prefer information as they adapt to the disease over time.

In the following paragraphs, I explore patient and practitioners' accounts of their perspectives on CML, how CML was managed by both, and whether the two issues were associated. I examine how patient and practitioner perspectives may relate to patient narratives, and coping mechanisms. The intention of this is to highlight the dichotomy between the complex effects of living with CML, and the idea that CML is a disease that is less complicated, and more manageable than other cancers.

8.6 CML perspectives

The patient interview analysis showed that most presented a positive attitude towards their disease, explaining they had reached a level of acceptance and were able to live a normal life, despite time since diagnosis, which varied between 2002 and 2016. This often seemed related to accounts of feeling lucky, as after the initial shock of a leukaemia diagnosis they learnt that CML is highly treatable, with a good prognosis. Many patients proposed that having a strong, positive personality and keeping active aided the acceptance process. I suggest this perspective is also supported by practitioner reassurance at diagnosis about the ability to lead a normal life, likely treatment success and normal life expectancy. Indeed, patients expressed their appreciation of such reassurance as a valued aspect of their practitioner care and relationship. Whilst patient reassurance is an essential aspect of care, it is also important to see that this positive perspective is formed by making comparisons to other haematological malignancies. Most practitioners reported CML as a rare disease, making up a small part of their workload. They tended to view the disease as stable, uncomplicated, treatable and with a good prognosis, with few patients becoming refractory to all treatments, relative to other haematological malignancies. Again, whilst this may also be an accurate view, further analysis of patient accounts revealed that several of the patients who portrayed a positive perspective also used language suggesting they struggled to maintain this, and had concerns and anxieties about future disease progression and premature or painful death. As discussed in the previous section, such psychosocial needs are often found to be unmet in cancer care with fears for the future and of disease recurrence being common in patients with haematological malignancies (Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013). In the case of CML, practitioners in this study seemed to be aware of psychological need yet less aware of some patient anxieties. Thus by giving a message of reassurance and normality they could unwittingly encourage patients to present themselves as feeling positive. However, patients may then continue to worry about their disease and future, and struggle to maintain normal living. This can extend to the way patients

manage their disease, which will be discussed in the next section. Later, I will explore the notion of chronic cancer and how this encapsulates some of the difficulties of living with CML with respect to its treatability and good prognosis, alongside challenges specific to cancer in general, such as fear of progression and early death. Initially, however, I will briefly review how sociological and psychological theory may partly explain why patient narratives appear to present a positive perspective on life with CML, despite the existence of psychological problems, before exploring how such perspectives may impact CML management.

8.6.1 Illness narratives, the biomedical model and coping

Lay narratives, such as those in the patient interviews, represent how individuals provide order to, and make sense of, their disease, and how it affects them within the context of their day to day life (Nettleton, 2013). They highlight biographical disruption described by Bury (2001) as the way in which one's life course and sense of self are altered by illness. The patient narratives in this thesis were somewhat similar, in that they focused on a series of disease-related events; the onset of disease, symptoms and effects on day to day life, which aligns with contingent and restitution narratives (Bury, 2001; Frank, 1995). It suggests that patient experience is aligned with the practitioners' view of CML as a stable disease. Although not initially part of the interview schedule, it was clear from the interviews that patients wished to give an account of their whole story, whilst emphasising their presentation, diagnosis and the start of treatment. This demonstrated the value of an open research question and an iterative approach to interviewing. Thematic analysis allowed participants to talk about what was important to them, rather than being restricted to specific topics within a formal protocol.

The patients' presentation of a restitution narrative, however, may not be fixed for each individual. Despite presenting an ordered set of events and impacts, interview data also suggested that disease related anxieties were shared by several patients, with some using language that indicated a struggle to maintain a positive perspective. This suggests a less predictable, emotional narrative more aligned to Frank's "chaos narrative" (Frank, 1995). The tension between these narratives could demonstrate how patients gave meaning to their disease. Use of the restitution or contingent narrative represents an attempt to give certainty to the disease, seeing it as the "consequences" it has on practical daily life, however the presence of struggles and anxieties suggest patients also apply a "symbolic" meaning to their disease, understanding it as an uncertain disease which cannot be cured and in which disease progression an ongoing risk (Bury, 2001). As Nettleton (2013) notes, such narratives not only describe the patient experience but can also influence that experience. Therefore, it may be that by presenting their story as a series of events and impacts, rather than

emotions or changes to the sense of self, patients are less likely to acknowledge and report the difficulties and challenges really concerning them. Such under-reporting, and difficulty reporting, was evident among interviewees regarding symptoms and non-adherence, with concerns about disease progression and the future also becoming evident despite positive narratives.

Patient narratives can reveal a lay understanding of health, which can enhance knowledge of how people care for themselves (Nettleton, 2013). In contrast to the traditional biomedical definition of health merely being the absence of disease, patients may view themselves as healthy despite living with ongoing disease (Bradbury, 2009). As discussed, patients interviewed for this thesis expressed this latter view, tending to present themselves as having a positive outlook on life despite living with cancer and experiencing symptoms/side-effects and anxieties. Much of the impact of CML was felt in terms of various activities in life such as employment, socialising, and hobbies, showing an understanding of health as something which enables us to carry out life roles. This highlights the shortcomings of understanding health within a biomedical model. Within this model, illness can be related to a pathology in a specific body part, which can be fixed within a medical speciality, so that health is achieved (Bradbury, 2009; Clarke and Everest, 2006) However, this does not consider the effect of the patients' social environment and underplays treatment side-effects (Nettleton, 2013), which is particularly problematic, as survival in CML is socially patterned (Smith et al., 2014), and side-effects were found to be prominent in the patient interviews, clearly impacting day to day life.

Much of the practitioner interview data around decision making in CML was concerned with the complexity of treatment decisions rather than those related to adherence, the management of chronic side effect or daily activities, yet it would be inappropriate to criticise practitioners for their use of the biomedical model. Prioritising medical treatment and the careful management of TKIs is clearly essential, due to evidenced survival gains. Furthermore, practitioners practice within the context of treating more acutely ill cancer patients and within the constraints of the NHS, which limits their clinic time. Therefore it is understandable that practitioners would have a biomedical focus; to ensure safe treatment decisions are made. Furthermore, although not always wholly mindful of the impact of CML and its treatment side-effects on some daily activities, practitioners overall had a broad awareness of the psychological state and socioeconomic circumstances of their patients. This suggests that whilst systematic constraints may mean that practitioner care is limited to a biomedical model, their discourse demonstrates a broader awareness of the patient's situation. However, the concern remains that as a result of this biomedical approach, non-adherence, symptoms and other concerns may go under-reported. Such sociological concepts are rarely investigated in haematological malignancies, as most studies involving the sociology of cancer focus

on patients with breast or gynaecological malignancies (Kerr et al., 2018). This is a situation this thesis begins to address.

Finally, expressing a positive perspective on life with CML, despite psychological struggles, may represent a way of coping, a concept described as the process people put in place to manage the impact of illness with the resources they have (Nettleton, 2013; Sarafino and Smith, 2012). Feeling 'lucky' or 'grateful' to have CML and expressing an optimistic outlook may represent the emotional mechanism of "re-defining" the stressful diagnosis into a more positive experience (Sarafino and Smith, 2012). This process is encouraged by some practitioners, and the benefit emphasised, when CML is compared to other more acute, life threatening haematological malignancies. Patient descriptions of their personality type as strong willed, positive and proactive, may also signify a higher level of self-efficacy, or confidence in using such coping mechanisms. Patient self-efficacy is very strongly associated with lower distress and higher quality of life (Chirico et al., 2017), suggesting that any disruption to their coping mechanisms may be detrimental to their psychological state and quality of life. Reassurance patients receive from practitioners at diagnosis may, therefore, be important in enabling coping, despite encouraging the idea that their cancer is a low key disease. The next section will explore disease management by patients and practitioners and how this may have been affected by their narratives and perspectives.

8.7 CML management by patients and practitioners

8.7.1 Adherence

Adherence to TKIs was discussed with patients in the context of how they managed their disease. Many of the findings in this thesis were comparable to previous studies, however some were unique to this analysis. Findings from the interviews will be discussed within the context of the wider CML adherence literature, followed by a discussion of patient and practitioner management of adherence. In my interview sample, the proportion of patients with any level of non-adherence was 88%, reducing to 31% for those who missed a dose less than once a month, with none missing more than three times a month. The practitioner group reported that most patients were adherent, therefore the situation is not wholly clear. This uncertainty is reflected in conflicting findings from the literature review in this thesis, non-adherence varying from 0-55% (Leader et al., 2018^a; Sacha et al., 2017; Yanamandra et al., 2017) and a lack of consensus reported on a safe cut off level for non-adherence. However, focusing on the level of non-adherence implies patients are either adherent or non-adherent, when in reality they are likely to display both behaviours over time. This is considered and evidenced below.

8.7.2 Reasons for non-adherence

Reasons for non-adherence in the current study can be categorised as unintentional and intentional as first described in relation to CML by Eliasson et al (2011), and now the accepted method of describing TKI non-adherence. Unintentional non-adherence was most common in this thesis, with many of the group describing this. It was most frequently due to forgetting, supported by similar findings in the practitioner interviews, thematic synthesis (Bolarinwa et al., 2018; Graffigna et al., 2017; Lim, Eng and Chan, 2017; Wu et al., 2015; Eliasson et al., 2011) and literature review (Rychter et al., 2017; Hosoya et al., 2015). Patients explained this was often due to a change in routine, being unwell or having other tablets to take, all of which could be compounded by the need to take the tablet around mealtimes. Unintentional non-adherence was often described as occasional, with changes in routine occurring due to holidays, socialising or travel, suggesting that adherence could change over time, depending on when these changes occurred. Patient findings did not reflect certain aspects of the thematic synthesis, such as unintentional non-adherence caused by the hospital system due to the cost of treatment and monitoring (Bolarinwa et al., 2018, Graffigna et al., 2017). This is reassuring in a country where TKIs are routinely available for NHS practitioners to prescribe, and supplied to patients free of charge.

Interestingly, the practitioner interviews revealed a further group of patients more likely to unintentionally not adhere to their medication. They described patients who lacked awareness, acceptance or organisational skills to take their treatment as prescribed. By miscounting, a lack of forward planning or struggling to comprehend instructions, patients may unintentionally miss their medication. Such reasons were not seen in the patient interviews, nor were they highlighted in the thematic synthesis or literature review. This may be due to patients being reluctant to describe this type of non-adherence in interview or patient questionnaire studies. Gathering data in this way is important as patients are best-placed to estimate of their own behaviour, as argued in the CML PRO literature (Efficace et al., 2014^b; Williams et al., 2013), however by adding practitioner accounts, I have highlighted other patient behaviour not captured by these methods. In addition, practitioners were able to describe socioeconomic factors which they believed may impact on adherence and interact with co-morbidity. The current study demonstrates the value of practitioner perspectives by revealing a group of patients not included in the sample, who could only be described due to the breadth of practitioner experience with CML patients.

Intentional non-adherence was less common in the patient sample, which was often due to medical instruction or side-effects. Findings from the thematic synthesis were unclear regarding side-effects, whereas this came across as a significant reason for intentional non-adherence in the literature

review. This highlights the benefit of larger sample sizes used in quantitative surveys, which have the ability to identify the prevalence of predictors of non-adherence. More practitioners reported side-effects as a common reason for intentional non-adherence, which could be compounded by co-morbidity and interact with socioeconomic circumstances. Few patients described intentional decisions to miss medication for other reasons; due to a social occasion or on the advice of an alternative practitioner. Again, these appeared occasional examples, supporting the idea that non-adherence may change over time. Practitioners also identified a group of patients who intentionally missed medication due to not wanting to take it. These patients were described as simply “not wanting” or “not liking” to take their tablets, to attend appointments or keep in contact, feeling they did not need medication or had difficulty accepting the disease. Practitioners went into detail about the characteristics of such patients, which included being more likely to be younger, having mental health problems, or have issues with drug/alcohol abuse. This group was not described in the patient interviews, thematic synthesis or literature review, again showing the benefit the practitioner perspective brings.

8.7.3 The management of adherence

Analysis of patient and practitioner interviews demonstrated the differing approaches to managing adherence. Patients largely discussed self-implemented strategies to remember their medication, whereas practitioners discussed how they identified non-adherence and the dialogue they had with patients to identify this. Many patients used daily routines as prompts to remind them to take medication, commonly mealtimes, which also served to control GI side-effects. This reflected findings from the thematic synthesis (Wu et al., 2015; Guilhot et al., 2013; Eliasson et al., 2011), as well as those from some practitioners who had advised on the timing of medication. Several patients explained that polypharmacy acted as a reminder, however the wider evidence is unclear. This was not noted in the practitioner interviews or thematic synthesis, and the literature review revealed a lack of consensus in quantitative studies about the effect of polypharmacy.

Several patients said family members reminded them to take their medication, reflecting earlier accounts on the importance of social support on experiences. The presence of family, friends and others in supporting adherence was also evident in the literature review (Sacha et al., 2017; Yanamandra et al., 2017) and shown to be valued in the thematic synthesis (Bolarinwa et al., 2018; Lim, Eng and Chan, 2017). However, such support, although present in practitioner accounts, was not emphasised, reflecting earlier discussion about practitioner awareness of the vital role such support plays in modifying patient experiences. Finally, patients frequently reported the use of a device, such a Dossett box, or alarm to organise and remind them about their medication.

Interestingly, although this was also evident in the thematic synthesis, there was no interview data regarding the use of devices or alarms in the practitioner interviews or the literature review. This perhaps suggests that such measures may be initiated by patients and/or that practitioners do not have standard advice on the use of such strategies. Some practitioners did explain their approach to discussing non-adherence with patients. This could be supportive, encouraging the patient to talk about reasons for their non-adherence, or more challenging and direct. Practitioners seemed to use both techniques. This provided an insight into the management of adherence not seen in the CML qualitative literature, and highlighted an apparent lack of standard approach across practitioners/hospital sites as to how adherence was to be managed.

8.7.4 Identifying and reporting of non-adherence

The identification and patient reporting of non-adherence was discussed by patients and practitioners, a theme which was also evidenced in the thematic synthesis. Commonly, non-adherence was suspected by practitioners after seeing a deterioration of the BCR-ABL results, reflected in the Wu et al (2015) study, or due to inadequate prescriptions being ordered or collected. Practitioners also identified non-adherence by directly asking patients, or by patients telling them. However, although several patients reported non-adherence incidents to practitioners, some did not, either because it was not thought to have effected disease response, they did not feel unwell, did not want to bother their doctor or felt it was too infrequent to report. Analysis of patient interviews also suggested that a lack of understanding in some areas of disease and treatment may have contributed to this. Unlike the Wu et al (2015) study, practitioners seemed aware that some patients did not report non-adherence, citing the same reasons as patients, but adding that some may deny non-adherence, again contributing knowledge not evident in the patient interviews or thematic synthesis. Overall, themes from the practitioner interviews suggested that a group of patients sharing certain characteristics of non-adherence were not sampled in the patient interviews and not present in the thematic synthesis.

Furthermore, as in other qualitative studies (Wu et al., 2015; Eliasson et al., 2011), practitioner advice may unintentionally support non-adherence. Some practitioners said they actively advised patients that it was acceptable to miss an occasional dose, perhaps basing this on a stable BCR-ABL response. Others were unsure if missing an occasional dose would significantly affect disease response and outcome, an uncertainty shared by some of the patient sample. This is in addition to an uncertainty reported by some practitioners about whether BCR-ABL results are actually a reliable indicator of non-adherence. These uncertainties could partly explain the varied advice patients received after reporting non-adherence.

8.7.5 Management of side-effects

It is clear from the analysis that treatment side-effects were significant for several patients, both in terms of how frequently they were experienced and the range of daily life activities affected. Whilst aware of the treatment side effect profile of drugs, and understanding that fatigue and GI symptoms were common, practitioners seemed to underestimate muscle cramps and pain. CML HRQOL literature has demonstrated how even symptoms regarded as low grade can significantly impact quality of life, and how patient and practitioner estimates of symptom burden may vary.

8.7.6 Patient and practitioner management of side-effects

Several practitioner interviewees described medical management strategies to deal with side-effects, such as switching TKI or prescribing supportive medication. They often explained the complexity of managing side-effects alongside co-morbidity and consequent polypharmacy. Patients however, appeared to focus on self-management strategies, including over the counter medication and learning to cope with symptoms. Some practitioners also explained the information they provided at diagnosis regarding side-effects, and the supportive approach they took in discussing symptoms with patients. Again, patient accounts differed somewhat, in that whilst most appreciated the disease related explanations given by practitioners and had a good understanding of some aspects of the disease, there seemed to be misunderstandings about side-effects, with several patients saying they struggled to effectively discuss symptoms with their practitioners. This suggests practitioners' efforts to control side-effects may not be fully realised by patients.

8.7.7 Reporting of side-effects

Several patients told of difficulties they had experienced in discussing side-effects with practitioners, which is reflected in the lack of awareness of side-effects reported by some patients. Reasons for this included it being a long time since diagnosis, side-effects potentially being due to co-morbidity, or fear regarding the discussion. Others were hesitant to consult their practitioners as they did not want to bother them in case were too busy, did not want to ask in case they were given more medication or felt they could cope by themselves. Several practitioners seemed to be aware that there was an under-reporting of side-effects, with patients seeing them as too busy, or patients themselves perceiving their disease as low level and therefore amenable to self-management. Interestingly, the side-effect most commonly self-managed was muscle cramp, which would explain a lack of reporting of this issue among practitioners. Patients were more likely to report GI side-effects, which practitioners were aware was common. These findings are somewhat similar to other chronic cancer studies, which also found a reluctance to report side-effects to oncologists, who may

be disinterested; patients feeling they had to accept symptoms as their treatment was lifesaving; or an acceptance regarding the self-management of chronic symptoms (Boele et al., 2019; Harley et al., 2012). Information about side-effects was also prominent in reviews of unmet needs in literature on haematological malignancies and other cancers (Hall et al., 2013; Harrison et al., 2009).

8.8 Summary: CML management and disease perspectives

The analysis of patient and practitioner interview data on adherence supports several findings from previous literature. Unintentional non-adherence was most common amongst patients, related in particular to forgetting and changes to routine. Intentional non-adherence was less common and often due to following medical advice or to avoid side-effects. Examples patients provided suggested non-adherence was infrequent and related to events which happened occasionally such as holidays and socialising, therefore indicating that adherence may vary over time, rather adherence or non-adherence being a fixed behaviour. However, the practitioners described two further groups of patients: those not adhering due to a lack of awareness, and those who did not want to take their medication; neither of which has been previously described in the CML literature, thus clearly demonstrating the value of acquiring practitioner perspectives. There may be some areas where practitioner awareness could be raised, particularly regarding the importance of social support and devices/reminders to support adherence. Perhaps one of the most concerning findings was the under-reporting, and difficulty reporting, of both non-adherence and side-effects. In terms of adherence, I suggest this may relate to a shared uncertainty, between patients and clinical staff, about the actual impact of missing medication occasionally and a consequent lack of consistency in practitioners' advice about this. This difficulty is enhanced by the absence of an identified cut off point for non-adherence, as noted in the literature review. Furthermore, formal advice on specific levels of non-adherence appears to be lacking. The widely used ELN guidance (Hochhaus et al., 2020) acknowledges the importance of discussing adherence with patients who do not respond to treatment, however it does not provide specific guidance on adherence advice, despite being the most commonly used guidance by practitioners.

Difficulties reporting side-effects appeared to relate to patient awareness about side-effects, difficulties in patient/practitioner communication, practitioner time-pressures, reluctance to take more medication, the presence of co-morbidities, and the perception that CML should be self-managed. Despite practitioners' accounts and literature recommending the need for information on side-effects (Hall et al., 2013; Harrison et al., 2009), continued misunderstandings amongst the patient sample may have impacted on reporting. This may be related to the way information is portrayed, with suggestions that it should be tailored to the needs of individual patients, presented

in a timely manner and in a way that is relevant to the impact of symptoms on daily activities (LeBlanc et al., 2019; Swash, Hulbert-Williams and Bramwell, 2018; Evans, Ziebland and Pettitt, 2012). A concept not identified in this thesis, and contrasting with studies recommending the need for more information/discussions, was that patients themselves may avoid discussing treatment effects or adherence as a way of coping, in order to maintain hope in the face of a cancer diagnosis (Atherton, Young and Salmon, 2017), or as a blunting mechanism in response to the stress of diagnosis (Rood et al., 2015).

The patient/practitioner relationship has been identified as key in patients' communication with their practitioner, and therefore is likely to affect the reporting of adherence and side-effects. Work investigating haematological malignancy patients in this area suggests the criteria for a good relationship involves trust, honesty, seeing the same practitioner, and practitioner interest in patients as individuals (Swash, Hulbert-Williams and Bramwell, 2018; Atherton, Young and Salmon, 2017). Lack of clinic time was identified in this literature, as a barrier to meeting needs, but was considered unavoidable when patients with more acute disease had to be prioritised, despite this resulting in less time to listen to the concerns of those with more chronic diseases (LeBlanc et al., 2019; Swash, Hulbert-Williams and Bramwell, 2018; Evans, Ziebland and Pettitt, 2012). Finally, several authors refer to the idea that some chronic haematological malignancies are perceived by practitioners, and patients, as low grade, less complex diseases which should be manageable by the patient. Wu et al (2015), for example, describe this as 'downward comparison', where patients see themselves as 'lucky' compared to those with acute, life threatening haematological malignancies. Patients with non-Hodgkin lymphoma (Swash, Hulbert-Williams and Bramwell, 2014) considered their lymphoma more like a chronic disease than cancer. Evans, Ziebland and Pettitt (2012) explain that the perception of practitioner lack of interest in CLL patients may be due to their advice that patients continue with their normal life, which does not grant them the 'sick role', and may discourage them from seeing side-effects or non-adherence as concerns to be raised in appointments. This idea is considered in the previous section of this chapter. Finally, practitioners perceived CML as a simple disease compared with other, acute haematological malignancies, and reassured patients of this at diagnosis. Whilst this may help maintain a positive focus and enable coping, it may also lead to under-reporting in these patients, and therefore unmet needs. In the discussion chapter, I will suggest that moving the focus and model of CML care away from the hospital context and towards understanding it as a chronic cancer or chronic disease, may enable patients to be better supported, thus allowing hospital practitioners to focus on patients with the greatest medical needs.

Chapter 9 Discussion and Conclusion

This thesis is the first UK qualitative investigation of the experience of living with, and managing, CML from both patient and practitioner perspectives. Whilst it supports previous qualitative evidence, it also presents significant original findings. The considerable impact of CML on employment and the importance of rich social support to patients were prominent. These aspects seemed to be somewhat underestimated by practitioners and were not major themes in other qualitative work. Co-morbidities were described in terms of their impact on patients' symptoms and daily lives, and on the increased complexity they could bring to CML treatment decisions.

The thesis findings also offer a unique picture of practitioners' perspective on their care of CML patients. Whilst there was lack of awareness into some aspects of the impact of CML, practitioners generally demonstrated a broad awareness of patients' socio economic context and psychological state. Practitioners identified two groups of patients less likely to adhere to their medication not identified in previous qualitative work: those who lacked disease awareness/acceptance or the organisational skills to take their medication, and those who did not "want" or "like" to take their medication. Uniquely, the thesis describes aspects of hospital care for CML patients and shows how these systematic factors may impact on their experience.

Of concern, were themes of patient under reporting, or difficulty reporting, non-adherence and side-effects, particularly given the impact the former could have on response, and against a background of widespread side-effects and their impact on impact on daily life. My findings also described the practitioner perspective on CML, seen generally as a low grade disease with a good outcome and successful treatment, and the patient perspective presented as a positive outlook on life. However, my analysis also highlighted patient anxieties for the future and struggle to maintain this positive perspective. Referring to theories of illness narratives (Bury, 2001; Frank, 1995), I was able to reveal a patient restitution narrative of a positive account of events reflecting the practitioners' view of the disease as predictable and low key, and the co-existence of a chaotic narrative in patient accounts, where anxiety exists over an uncertain future. The restitution narrative offers patients some crucial reassurance and predictability in the face of a cancer diagnosis, and is encouraged by practitioners' messages that their disease is less complex and has a good prognosis. However, I suggest that failure to consider their chaotic narrative may discourage them from reporting side-effects and non-adherence, which ultimately may impact on both quality of life and disease response.

This chapter extrapolates my findings further by considering them within broader concepts in cancer, policy and practice. Definitions of chronic cancer are explored in a limited area of research, and are considered in relation to CML and other haematological malignancies. Many patient needs

in these groups are found to be shared with other chronic cancers, despite their different medical and epidemiological features. The chronic cancer experience relates to that of chronic illness, and therefore may be suited to a model of self-management often applied to those living with longstanding illnesses. This model is prominent in Department of Health (DOH) cancer survivorship initiatives. Concepts of chronic cancer, self-management, survivorship, and shared care in relation to CML are discussed in this chapter. I argue that the language used in survivorship documentation may lack relevance to CML and some other haematological malignancies, and explore criticism regarding the application of models of self-management to cancer patients, due to the responsibility this places on the individual by failing to consider their context. This may explain the limited research examining survivorship initiatives in haematological malignancies, which is then explored.

Finally, I examine the evidence which is available suggesting shared care with primary and/or palliative care services may be suitable for patients with haematological malignancies, although such care requires strong coordination and shared care plans. In this section, I argue that sharing follow-up care with community services may encourage patient reporting by adjusting their perspective of their disease from within the hospital setting to one within their own community context. This implies a potential shift in understanding CML may be beneficial, which connects with debates about self-management and survivorship.

9.1 Chronic cancer and CML

Cancer prevalence is increasing and the number of cancer survivors is set to rise. In the UK, Maddams, Utley and Møller (2012) predicted that the number of patients alive following a cancer diagnosis would increase by around one million every decade until 2040. This includes those living with CML, where prevalence based on contemporary data, estimates that almost five and a half thousand people diagnosed within the last 10 years are currently living with this cancer in the UK (HMRN, 2021^b). Increasingly, many cancer patients will be treated with targeted or supportive therapies which, similar to TKIs for CML, may be oral treatment self-managed by the patient at home (Boele et al., 2019). Although CML is a unique disease compared to other haematological malignancies due to its chronicity, other sub-types also require self-managed treatment, such as myeloproliferative disorders, treated with ruxolitinib, or relapsed myeloma, controlled with lenalidomide.

Although definitions of chronic cancer are said to be lacking (Frick et al., 2017; Harley et al., 2012), authors broadly suggest the term applies to those living with long-term cancer, managed by ongoing treatment, who may not reach a post-treatment stage, or who experience chronic symptoms related to cancer treatment; people living with metastatic or relapsed disease, or a cancer that may reoccur

(Pizzoli et al., 2019; Gerbino, 2014; Berlinger and Gusmano, 2011). As discussed, UK work by Harley et al (2012, 2019) extended awareness of chronic cancer needs by developing the CCEQ. This team described chronic cancer as one of advanced or metastatic disease, which “cannot be cured”, a cancer where treatments to “control symptoms, slow the disease or prolong life are available”, and where the patient “is not considered to be at the end-stage of cancer”. Although CML falls within these definitions, difficulties arise as this description encompasses many heterogenous cancers, trajectories and treatments (Hall et al., 2013), reflected within haematological malignancy subtypes (Frick et al., 2017), which may create challenges for implementing care.

Despite broad definitions, patients with chronic cancer share particular needs and difficulties, reflecting the long-term nature of their illness, including frequent hospital visits and long waiting times, a significant symptom burden, needing help with daily practical tasks, changes in employment, concern over uncertain futures and difficulty accessing support services (Boele et al., 2019; Harley et al., 2012). These patients are also more likely to experience treatment effects than those receiving curative therapy (Frick et al., 2017). Concerns about disease recurrence and the future, and information about this, were a significant theme in reviews specifically examining the needs of haematology patients, although these included people at an early treatment stage (Swash, Hulbert-Williams and Bramwell, 2014; Hall et al., 2013). This thesis, together with CML literature on symptom burden and quality of life, concurs with these findings, particularly regarding the significant, ongoing symptom burden, anxieties over the future and employment effects. As discussed in the introduction, CML and chronic cancers may also share characteristics with those living with chronic illness (Pizzoli et al., 2019; Berlinger and Gusamo, 2011) and therefore models of self-management in chronic illness may be of relevance to the care of these diseases. The use of self-management within CML and cancer care will be considered in the following section.

9.2 Chronic illness and self-management

The definitions of self-management from the chronic illness literature described earlier (chapter one: self-management) (Lorig and Holman, 2003; Barlow et al., 2002; Corbin and Strauss, 1988) presented this concept as a holistic set of tasks which reflects the findings of this thesis, including how patients manage the medical aspects of CML, such as medication adherence and side effects, adapting to changes to daily life tasks, and a change in emotional perspective on life. My findings support these definitions, in that patients and practitioners described not only how they managed adherence and side effects, but also explored the psychological and practical impacts of the disease and treatment. The thesis also supported self-management theory in the value of good patient-practitioner relationships, and the influence of health system factors on patients’ self-management (Lorig et al.,

1999; Wagner, Austin and Von, 1996). However, these definitions also suggest the patient should take on responsibility for their own self-management (Lorig and Holman, 2003), and perhaps overlook the influence of the patients' wider social context. A strong theme in the thesis findings was the value of social support in the disease experience, patients placing great emphasis on the crucial role that this plays, including family, friends and employers through, for example, the sharing of emotions and providing advocacy. Self-management in cancer care is reported to aim at increasing responsibility of the individual patient for their health and reduce the dependency patients have on their medical team (Taylor, Chan and Monterosso, 2015). However, the use of this notion in self-management interventions can lead them to be less effective (Ellis et al., 2017; Morden, Jinks and Ong, 2012; Atkin, Stapley and Easton, 2010). Authors contend that such self-management interventions take on a neoliberal discourse, by placing responsibility for health on the individual (Ellis et al., 2017; Morden, Jinks and Ong, 2012) and ignoring the influence of social context (Ellis et al., 2017; Vassilev et al., 2014). This raises difficulties as decisions about disease management and the meaning individuals place on their illness can all be influenced by their social context (Ellis et al., 2017; Atkin, Stapley and Easton, 2010). Furthermore, the extent to which the self-management model of care is applicable to cancer patients has been questioned, highlighting that there is little research exploring how self-management should be conducted, and noting that some survivors may struggle with this approach (Foster et al., 2018).

My findings regarding the need to take account of context are supported in a systematic review that also identified the importance of social support to cancer patients in the "restorative" phase of survivorship, arguing that this contradicts the individual nature of self-management models in chronic illness (Boutillier et al., 2019). A further a review of qualitative research exploring the needs of patients self-managing chronic disease revealed that several types of support were required; informational, psychosocial, and most importantly relational, and that this should be delivered by different groups of people including practitioners and family (Dwaarswaard et al., 2016). It is therefore argued that people cannot self-manage alone and features of relational support, such as sympathy and partnership, are vital to enabling other types of support to be accessed (Ellis et al., 2017; Dwaarswaard et al., 2016). In a review of self-management interventions for those with chronic disease, socioeconomic status was found to influence effectiveness, potentially widening any existing social gradient (Hardman, Begg and Spelten, 2020) and further demonstrating the impact of social context. Self-management is a key component of the National Cancer Survivorship Initiative (NCSI), a collaboration between the DOH and MacMillan (Department of Health 2010). Survivorship, and its relevance to CML will now be explored.

9.3 Survivorship

The NCSI vision was created as a result of an increasing prevalence of people living with and beyond cancer, and growing evidence of unmet need in this population (Department of Health, 2013). The “Living with and beyond cancer” documents (Department of Health 2010, 2013) provide guidance to commissioners and practitioners on actions to facilitate a move towards recovery and health after treatment, personalised assessment and care planning, self-management, tailored follow-up care and the use of patient reported outcome measures (PROMs). Many initiatives have been implemented across the UK and the YHHN area, including a programme run by Hull University Teaching Hospitals, which includes individual assessments, telephone support, exercise programmes and return to work events (<https://www.hey.nhs.uk/queens/services/survivorship/> 2020).

Much of the NCSI guidance has relevance to the experience of those living with CML, including patient education programmes about available services, changes in hospital follow-up to “sustained recovery”, and the use of PROMS to assess the long-term “consequences of treatment”. Although applicable, however, much of the language refers to care at the “end of treatment” and the most relevant actions, contained within the theme “supporting people with active and advanced disease”, frequently direct their aims to patients with recurrence or metastatic disease (Department of Health, 2013). The Hull initiative states that the service is intended for any “patient who has completed cancer treatment”, although it is unknown if this is strictly followed. Importantly, CML patients, as well as those with other indolent haematological malignancy subtypes are unlikely to be at an “end of treatment” stage, although the latter may experience recurrent disease as part of their relapsing-remitting trajectory. Whilst survivorship initiatives are obviously a positive step in meeting the long-term needs of cancer survivors and reducing the acute oncology workload, the needs of CML patients, living with what is essentially a chronic cancer, do not seem to be fully considered. Though the notion of survivorship in CML seems very relevant due to its long-term chronicity, it is questionable if this disease fits current understanding of the term, or if the self-management model is appropriate. Next, CML will be considered within literature addressing survivorship in other haematological malignancies and chronic cancers.

9.4 Survivorship care and haematological malignancies

Chronic cancers and haematological malignancy subtypes are thought to be under-researched in the survivorship literature (Taylor, Chan and Monterosso, 2015; Harley et al., 2012; Berlinger and Gusmano, 2011). A large USA study analysing online survivorship care plans, completed by patients and practitioners, found that those with chronic cancer were more likely be cared for solely by oncologists without primary care involvement; less likely to have practitioner input into their

survivorship care plan; and were less satisfied with their care plan, than patients treated with curative intent (Frick et al., 2017). In the UK, a review found only six studies based on models of survivorship care used in haematological practice (Taylor, Chan and Monterosso, 2015). The authors found care models were generally physician, nurse or shared care led, and that lack of outcome measurement and variability in the type of care made comparison difficult. Furthermore, barriers exist to the implementation of survivorship care in the haematological malignancy setting. Langbecker et al (2016), for example, report that the nature of these cancers, in terms of understanding the start point of survivorship made implementing survivorship care difficult, but that factors such as clear professional responsibilities, a named coordinator, a team approach and good information communicated across the team were seen as facilitators to change. Wallace et al (2015) reported that nurses viewed themselves as key to the provision of survivorship care for haematology patients, but noted areas where skills needed to be developed, such as fertility issues, and systematic barriers that needed to be overcome, such as a lack of time and limited patient educational resources.

Currently, CML follow up care, and that of many other chronic cancers, remains hospital based, with such settings being historically well set up to provide acute cancer treatment and monitoring for recurrence. However, hospital may be less well equipped to meet long-term patient needs for psychosocial, emotional and practical care (Maher, Velikova and Betteley, 2015; Harley et al., 2012; Berlinger and Flamm, 2009). Gerbino et al (2014) argue cancer services need to rethink their approach to chronic cancer care and agree an “ethical framework” for these patients. Taylor, Chan and Monterosso (2015) concluded from their review that the shared care model may be most acceptable to practitioners and patients with a haematological malignancy, as it incorporates the expertise of different professionals, including primary care staff, which reinforces the notion that there must be an all-round willingness to apply this model, and that communication and coordination are key (Taylor, Chan and Monterosso, 2015). Shared care models, and their use within cancer survivorship will now be explored further.

9.5 Shared care models and cancer survivorship

Shared care may reflect the direction of future chronic cancer care, given a rising prevalence and increasing pressure on acute services, as well as potential GP involvement in survivorship care, as is recommended in “Living with and beyond cancer” documents (Department of Health 2010, 2013). Much of the evidence around shared care originates from the chronic disease management literature. In an early survey of shared care models used by the NHS in Scotland and London, predominantly for chronic disease management, Hickman et al (1994) described this care as:

“The joint participation of GPs and hospital consultants in the planned delivery of care for patients with a chronic condition, informed by an enhanced information exchange over and above routine discharge and referral letters” (Hickman et al., 1994, p. 447)

The authors found that shared care designs differed and created a taxonomy of these models, classifying them as: community clinics, run by specialists in general practices; a basic model, involving an increased level of letter based communication between hospital and GP; a liaison approach, where hospital and primary care teams meet regularly to discuss a patient's management; a patient held paper shared care record; computer assisted shared care information exchange and the use of electronic mail, where certain data is collected and shared at each clinic attendance. More recent reviews of chronic disease shared care models have demonstrated an increasing complexity in how such care is organised (Mitchell et al., 2015; Smith et al., 2007). A Cochrane review found that most of the twenty included studies showed shared care interventions had multifaceted designs and included clearly defined roles, clinical and referral protocols, and co-ordinated patient records (Smith et al., 2007). Mitchell et al (2015) provided a further updated review of studies examining shared primary/secondary care for those with chronic disease. The authors again demonstrated an increasing complexity of the shared care model and identified six shared elements: interdisciplinary teamwork, depending on clear role definition and the correct skill mix; communication/information exchange, underscored by a willingness to share information; agreed shared care guidelines/pathways; initial training, for primary care professionals and ongoing for patients; improved access to care for patients, such as reliable parking and reduced waiting appointment times, and a secure funding model.

The effectiveness of shared care models in chronic disease management is variable. Smith et al (2007) found a lack of improvement in most outcomes (e.g. physical/mental health levels, psychosocial measures, number of hospital admissions). However, there were significant gains in terms of medication adherence and appropriate prescribing for those patients within a shared care model (Smith et al., 2007), two areas of critical importance to the management of CML patients. More positive results were found in the Mitchell et al (2015) review, the authors concluding that no study found a negative impact on outcomes, and although there was no substantial impact on clinical measures, a significant effect on “process of care” outcomes was found, including improvements in measures such as hospital attendances, patient satisfaction and GP use of shared records and disease registers. This has further implications for those with CML, who in this study reported difficulties with hospital processes involved in their outpatient follow up care.

The evidence base for shared care within the management of cancer survivors is limited. A systematic review revealed a lack of consistency in model design between the included twelve studies (Zhao et al., 2018). Shared care interventions were all reported to be “complex” and included the introduction of variable levels of primary care practitioner (PCP) follow up visits to replace or add to hospital visits, providing PCPs with an education package, cancer centres providing PCPs with guidelines for ongoing care, enhancing communication between hospital and PCPs, and providing PCPs with a register and recall system (Zhao et al., 2018). Although the included studies showed no significant impact on physical/psychological and economic outcomes, a substantially higher level of patient satisfaction in those receiving this model of care (Zhao et al., 2018).

Overall, the chronic disease and cancer survivorship shared care literature suggests a complexity in how this care is designed, making it challenging for practitioners and policy makers to decide on the best model for their service. Whilst Mitchell et al (2015) suggest future trials of shared care should focus on elements of interventions which have been found to be effective, Nekhlyudov et al (2017) provide some further clarification of shared care design in their scoping review examining the integration of primary care providers into cancer survivorship care. These designs range from an intervention focussed primary care model which concentrates on the provision of a shared care plan, to a higher level of integration by PCPs, such as the long term follow up clinic design where the PCP is integrated into the oncology or survivorship follow up clinic (Nekhlyudov et al., 2017). In addition to a lack of clear evidence for the use of shared care models in cancer survivorship, studies have shown that, as with models of survivorship care in haematological malignancies, barriers exist to their implementation, such as lack of communication with secondary care providers and differing attitudes towards shared care between primary and secondary care physicians (Cheung et al., 2013; IJstrand et al., 2020). Nekhlyudov et al (2017) suggest various factors likely to support the integration of PCPs including: educating PCPs in core competencies, the development of clinical practice guidelines, risk stratification for patients to decide what level of integrated care is optimal for them, examining the clinical workforce and considering the involvement of nurse practitioners and physician assistants, and considering financial incentive for PCPs to become involved. Patient acceptance of the shared care model may be a further important consideration, and could reflect how they view the care offered by their PCP, which within the UK is frequently their GP.

Studies found some chronic cancer patients felt their GP did not have the expertise to manage their needs, and 43.5% never or rarely visited their GP (Boele et al., 2019; Harley et al., 2012). In this thesis however, CML patients generally spoke positively about their GPs, particularly regarding efficiency in the time leading up to diagnosis, and their relationship with their GP. Practitioners also

found working with GPs to be of value, especially when managing co-morbidities or side-effects, suggesting that shared care may be seen positively by these CML patients and practitioners. Involving palliative care services in survivorship care has been suggested as ideal for chronic cancer patients, due to its focus on the individual, the impact the disease has on patients' daily lives and physical, emotional and psychosocial symptom management (Maher, Velikova and Betteley, 2015; Gerbino, 2014; Berlinger and Flamm, 2009). The involvement of palliative care in the management of chronic cancer may be difficult to accept for some CML patients, and careful planning and communication would be required to promote its value. However, there is little evidence for the integration of palliative care into chronic cancer follow up. On database searching no studies were found evaluating interventions sharing palliative care with secondary care for chronic cancer patient follow up. When considering changes to follow up care for CML, it is perhaps wise to be cautious. Although meeting definitions of chronic cancer, CML patients require ongoing specialist disease monitoring and, as practitioners reported, complex treatment decisions. Patients interviewed for this thesis greatly appreciated the relationship they had with their hospital practitioner and the reassurance this provided. To remove such support totally would risk the disease being inadequately monitored and may harm coping strategies. A design where care is shared is co-managed (Nekhlyudov et al., 2017) with patient visits split between primary care and hospital specialist care may be the most appropriate. Literature exploring barriers and facilitators to shared care can support the implementation of such a model of care.

The literature summarised in this section suggests that shared care models have become increasingly complex over time. Studies measuring the effectiveness of these models have shown varied results within the chronic disease and cancer survivorship literature, although notably there was some evidence of shared care improving medication adherence, appropriate prescribing, care processes and patient satisfaction, all of relevance to patients with CML. This thesis suggests that despite concerns over the complexity and effectiveness of shared care, such a model remains suitable for those with CML. Many patients in this thesis maintained a positive outlook but several held anxieties about their future, and underreported or had difficulty reporting, both non-adherence and side-effects. A model of shared care where patients are seen in a community setting (either primary or palliative care), focussing on the impact of their disease on daily activities and offering emotional and practical support, could help patients perceive their disease differently. In this context, both patients and community practitioners, be it primary care or palliative, may be more inclined to perceive CML as its impact on the individual and within the patient's home setting, rather than comparing to other more acute haematological cancers. This may provide patients with the confidence to discuss non-adherence and side-effects with community practitioners, and through

collaborative working with hospital practitioners, find solutions which work for them, within the context of their lives.

9.6 Implications for policy and practice

Whilst practitioners were well aware of many aspects of the patient experience, there were issues where they seemed to have less insight. The latter included awareness of the frequency with which muscle cramp and pain were experienced; the broader impact of CML on day to day activities, in particular work, but also generally getting out and about and pursuing hobbies and interest; and the importance of different types of social support from family, friends and others in buffering this impact. Patients may present a positive perspective on life and a restitution narrative of their disease experience, however, practitioners may lack knowledge of their struggle to maintain this and of hidden disease related anxieties. Practitioners seemed aware of some under reporting of non-adherence and hesitancy reporting side-effects by patients, but may have been less aware of reasons patients provided for this, such as not wanting to be prescribed more medication for a side effect or feeling the infrequency of their non-adherence would not be of concern to their practitioner. Finally, practitioners seemed less aware of patients' use of devices and reminders to support adherence, self-care methods to manage side-effects and the internet as a source of disease related information. However, in all other areas, practitioners demonstrated a broad understanding of patient experiences of CML, including the psychological impact, and potential treatment interaction with co-morbidity; they also understood patients' socioeconomic circumstances and the complexity of adherence. This suggests no indication for additional practitioner education, rather that the results of this study may raise awareness among some practitioners who, like those interviewed, have less time than they feel is required to fully discuss patient concerns.

At a system level, there was some inconsistency and uncertainty in the advice practitioners provided regarding non-adherence. It may be useful for guidance to be agreed at a regional level, on what practitioners should tell patients about the importance of regular adherence and remedial action that should be taken if medication is missed. The level of under reporting, or difficulty/hesitancy in patient reporting non-adherence and side-effects was troubling, and clinic time appeared inadequate for holistic discussion, despite the value patients placed on their relationship with practitioners. Incorporating extra time into clinics may help support reporting and generate an understanding of why this does not always occur. Finally, systematic issues such as inadequate pharmacy supplies, insufficient hospital parking and delayed or missing letters and results, could all impact on quality of life and how patients manage their disease. Later expert consultation supported this and described it as a central, rather than peripheral, issue affecting their disease experience.

Removing or resolving such obstacles may reduce the overall disease impact, in addition to improving the efficient use of practitioner time.

Regarding UK policy, current understanding of cancer survivorship does not fully incorporate all the features of chronic cancers such as CML and some other haematological malignancies, which may lead to patient exclusion from survivorship initiatives and services. Indeed, in this context, it is perhaps timely for policy makers to re-think definitions of survivorship, so that they incorporate the characteristics of cancers such as CML, which are increasingly treated in the longer term but may never be cured. I have suggested that issues with patient reporting of symptoms and side-effects is related to belief that CML is a relatively straightforward disease that can be largely self-managed and should not interfere significantly with normal life. Whilst this is an accurate view within the context of hospital cancer care, a shift in the location of care may encourage patients to report concerns more openly to their practitioner. Shared care with primary or palliative care services would be a major change to the way CML patients are followed up and considering the lack of strong evidence base, would require a feasibility study, in order to plan the trial of this new service, as is discussed later. However, such a service would balance the need for careful clinical follow up of treatment response by a CNS and/or consultant haematologist, with that focused on improving quality of life through managing side-effects and symptoms, caring for psychosocial needs and involving the patients social support network. The latter could be provided in the patients' home or a community setting and whilst this service would be available to all patients, input would vary depending on the primary/palliative care assessments. The model of care would require close collaboration between primary and secondary care sectors, as inevitably patient needs, such a pain management, will require expertise from both. Therefore, communication pathways would need to be clear and reliable, for example, through dedicated MDT meetings as advocated by the literature around shared care in cancer survivorship (Zhao et al., 2018; Nekhlyudov et al., 2017).

Two factors need to be considered when discussing implications for future practice; the discontinuation of TKIs, and the impact of Covid-19. Following results from large clinical trials (Hochhaus et al., 2020), the most recent ELN guidance maintains that treatment free remission (TRF) is now a realistic goal for CML patients. This guidance, alongside UK and USA specific guidelines (Smith et al., 2020; Radich et al., 2018), sets out criteria to support practitioners in decision making around the safe discontinuation of TKIs. The ELN vision is to see an increasing number of patients living treatment free within the next five years (Hochhaus et al., 2020), implying that frequent medical follow up may eventually not be required. However, at present, all patients initially require TKIs to attain the level and length of response required to discontinue medication, followed by increased testing for several years after stopping TKIs. Whilst adherence would no longer be an issue

and side-effects should improve, the experience of patients who have stopped treatment is not clear; including if they will share any concerns as those currently on TKIs, such as anxiety around disease progression and reduced quality of life. Furthermore, some trials reported up to a third of patients developing a “withdrawal syndrome”, describing predominantly musculo-skeletal pain, in the first weeks and months following discontinuation. Therefore, there remains a need for careful clinical observation of these patients and monitoring of ongoing patient need, particularly in terms of symptom management.

Since interviews were completed for this thesis, the Covid-19 pandemic has had a massive impact on the NHS leading to most haematological malignancy clinic appointments taking place via teleconferencing, and extended intervals between some blood monitoring (Willan et al., 2020). This was essential to re-direct NHS resources and protect those more at risk of serious illness due to the virus; people with haematological malignancies being more at risk of death from the virus than the general population (El-Sharkawi and Iyengar, 2020). As noted in the practitioner interviews, some patients in the YHHN area were already being monitored remotely by an outreach service for indolent haematological malignancies, such as untreated CLL and MGUS (a pre-cursor condition). As part of this process, the blood samples are taken at the patient’s GP surgery, prior to it being reviewed by a specialist scientist at the hospital, the results of which are then sent to the patient. This has resulted in the successful continuation of accurate disease monitoring, safe referral back to hospital when required, and patient satisfaction due to avoidance of prolonged waiting times in outpatient clinic (Rawstron et al., 2007). Outreach monitoring and the current remote monitoring of CML patients ensures that the disease is safely observed, however care remains within hospital setting and focus remains within the hospital context. I have suggested that setting up shared care with primary/community palliative care services, with clear coordination and shared care planning, could facilitate a shift to community health care settings and encourage the reporting of wider concerns and symptoms. It would also reduce pressure on hospital services by minimising telephone appointments at this unprecedented time. However, now more than ever, the NHS and its cancer services are dealing with a rebound of cancer patients, including those who did not, or were not able to, present at peaks of the pandemic (Willian et al., 2020), meaning now is not likely to be the optimum time for radical change.

9.7 Implications for future research

Findings from this thesis reflect the lack of a definition in the literature and clinical guidance of a critical level of non-adherence. There was uncertainty among patients and practitioners about whether missing an occasional dose was safe, and a lack of consistency in advice provided by

interviewed practitioners about adherence. Future research would be useful in identifying a consensus on the level, if any, of non-adherence which is clinically safe and unlikely to impact on outcome.

This thesis identified unmet needs among patients due to difficulty/hesitancy reporting, a lack of awareness in some disease knowledge, communication difficulties or disease perspective. Surveying a larger sample of CML patients, using the CCEQ or SUNS tool, would identify patterns of need across the region, areas of the greatest unmet needs and any associated sociodemographic factors.

Including and identifying those who are discontinuing their TKIs will also further understanding about the needs of this new population of CML patients.

As discussed, suggesting any change to NHS practice such as shared care of CML patients may not be feasible until the impact of Covid-19 on the NHS has reduced. However, a feasibility study examining the possibility of an intervention to share care for some CML patients with primary or palliative care services could be possible. This would be guided by evidence such as that summarised earlier from the cancer/chronic disease shared care literature, closely align with survivorship initiatives, and involve work to determine the features of shared care planning and coordination, guidance on re-referral into hospital systems, the willingness of practitioners to recruit patients, and capacity among primary care and palliative care services.

9.8 Strengths and limitations

This thesis, exploring CML from a patient and practitioner perspective has generated several unique findings. It has highlighted areas where practitioners may have less awareness of the problems faced by patients, and contextualized patient and practitioner views. Although efforts were made to include those who may have more complex issues and needs through purposive sampling, the patients who agreed to interview may not have represented the entire CML population, and might indeed have missed those with poor adherence. However, practitioner interviews provided insights into the characteristics of this group. Furthermore, it was not possible to provide representational generalisation of the practitioner sample, as the total group in the area was unknown. However, it may have been futile to sample practitioners with little experience of caring for CML, as they would have had little to offer in terms of describing care provision. Also, although I was unable to recruit at two of the local hospitals, the practitioners I did interview were representative of the YHHN area, in terms of the proportion working at local or cancer centre hospitals.

Despite being a qualitative study interviewing a small number of patients and practitioners, several of the findings are evidenced in the wider literature and participants were representative of the YHHN CML patient population, as a whole, which provides confidence that my results have some

transferability. In qualitative research, transferability is more important than generalizability, and I believe it highly likely that findings from described here are transferable to other locations and countries, with similar health care systems.

On reflection, the analysis may have benefited from attempts during sampling to match practitioners with the patients they cared for. Although I have compared patient and practitioner data, differences in their accounts could be due to variations in practice and patient need in different areas. However, the thesis was not focussed on investigating individual differences, but describing an overall experience of living with, and caring for CML. The thesis may also been strengthened by comparison of CNS accounts with consultant accounts of the care they provided to CML patients, as this was possibly influenced by cultural differences between the nursing and medical professions. However, I compared responses from each group, within a selection of themes, and found no clear distinction between the two professions, therefore decided any difference was unlikely to be present within my data.

Conducting the study within the infrastructure of YHHN had many benefits. Initially, I was able to sample patients who had already agreed they could be contacted for research purposes, which meant I was able to select individuals who were representative of the CML population in the geographical area, in terms of hospital type, gender and age at diagnosis. I was also able to contact patients from a local YHHN affiliated support group and gain valuable feedback on the proposed interview schedule, as well as comments on my findings. Finally, my work as a YHHN nurse meant I could access clinical staff I already had a professional relationship with, and their knowledge of other YHHN practitioners across the region facilitated snowball sampling.

I originally intended to conduct a mixed methods study, with qualitative interviews and a survey, to examine “sociomedical factors and survival in CML”. However, my iterative approach facilitated re-consideration of the study aims which, following the literature review, revealed broader issues in the CML experience, beyond those related to adherence, and the need to explore this from patient and practitioner perspectives. After discussion with my supervisors and TAP members, my aims were revised to include a broader contextual exploration of CML experiences, of which adherence is a part, suited to qualitative interviews and thematic analysis. My literature review, however, still contains some of the relevant subjects explored whilst considering my initial aims. Although sole use of qualitative methods somewhat limits the generalisability of my findings, this is compensated by the depth of information generated from interviews, the unique themes identified in the analysis, and the transferability of my results, made possible by using a representative sample of patients from a single large area, and locating findings within the wider literature.

9.9 Dissemination of findings

This thesis has been presented to different audiences at various stages of its development. For example, I shared the study plan and initial patient findings at regional haematology CNS meetings, to an MDT meeting at YHHN hospitals, and to colleagues within the Department of Health Sciences at the University of York. In 2018, I presented my work to charity supporters at a national grant holders' conference, organised by YHHN funders Bloodwise, and in 2020 I published a peer-reviewed paper, based on my thematic synthesis, in the *European Journal of Oncology Nursing* (Hewison et al., 2020) (see Appendix 4). On completion of my thesis, I plan to disseminate findings via a local haematology patient support group, as well as writing a lay-update for the YHHN patient website and newsletter. I aim to disseminate to YHHN practitioners by presenting my work across the network, via MDT and CNS meetings, and at local and national conferences. I also envision further publications in peer-reviewed journals, which will address findings from the patient/practitioner interviews.

9.10 Conclusion

This thesis sets out to define the patient and practitioner experience of living with, and managing treatment for adults with CML. It has produced unique findings, whilst also confirming the work of others. Importantly, it notes the significant impact CML may have on patients' lives and suggests that features of patient context and the care system can buffer this impact. Practitioners were aware the socioeconomic context of many of their patients, but lacked some awareness of the impact on CML on daily life, and some issues relating to self-management. Uncertainty, and an absence of a standard approach to non-adherence was noted, which likely relates to a lack of consensus about absolute adherence levels required. A shared perception of CML as a stable, treatable disease that should not impact on normal living was found to be reassuring to patients, but could discourage the reporting of side-effects and emotional concerns, as patients could view themselves as being responsible for managing these complaints. Difficulty reporting symptoms is concerning in a disease that shares many features with other chronic cancers, and diseases lived with over a life time.

Survivorship initiatives have great potential to meet the long terms needs of CML patients, however risk excluding them from such care by referring to survivorship as phase experienced by those at the "end of treatment", a point that currently most CML patients do not reach. Such initiatives centred on the self-management model are often applied to chronic illness. Whilst this concept acknowledges the wide ranging impact of CML, it is criticised for focussing responsibility onto the individual which disregards their social context. This context, however, can have a significant influence on how patients manage their disease, an obvious aspect being the importance of rich

social support identified in this thesis and in the wider literature. Shared care models may reduce demand on acute services, and shift focus of disease into the setting of the patients' home life and context, thus preventing comparison to more acutely ill haematological malignancy patients in the hospital setting. I suggest this will encourage patients to view their disease from a different perspective, in which they are more able to reveal emotional and physical concerns that can be resolved in partnership with hospital and community practitioners.

Appendix 1 Mixed Methods Appraisal Tool (MMAT)

Pluye, P., Robert, E., Cargo, M., Bartlett, G., O’Cathain, A., Griffiths, F., Boardman, F., Gagnon, M.P., & Rousseau, M.C. (2011). Proposal: A mixed methods appraisal tool for systematic mixed studies reviews. Retrieved on [date] from <http://mixedmethodsappraisaltoolpublic.pbworks.com>. Archived by WebCite® at <http://www.webcitation.org/5tTRTc9yJ>

PART I. MMAT criteria & one-page template (to be included in appraisal forms)

Types of mixed methods study components or primary studies	Methodological quality criteria (see tutorial for definitions and examples)	Responses			
		Yes	No	Can't tell	Comments
Screening questions (for all types)	<ul style="list-style-type: none"> Are there clear qualitative and quantitative research questions (or objectives*), or a clear mixed methods question (or objective*)? Do the collected data allow address the research question (objective)? E.g., consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components). 				
	<i>Further appraisal may be not feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.</i>				
1. Qualitative	1.1. Are the sources of qualitative data (archives, documents, informants, observations) relevant to address the research question (objective)?				
	1.2. Is the process for analyzing qualitative data relevant to address the research question (objective)?				
	1.3. Is appropriate consideration given to how findings relate to the context, e.g., the setting, in which the data were collected?				
	1.4. Is appropriate consideration given to how findings relate to researchers' influence, e.g., through their interactions with participants?				
2. Quantitative randomized controlled (trials)	2.1. Is there a clear description of the randomization (or an appropriate sequence generation)?				
	2.2. Is there a clear description of the allocation concealment (or blinding when applicable)?				
	2.3. Are there complete outcome data (80% or above)?				
	2.4. Is there low withdrawal/drop-out (below 20%)?				
3. Quantitative non-randomized	3.1. Are participants (organizations) recruited in a way that minimizes selection bias?				
	3.2. Are measurements appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding the exposure/intervention and outcomes?				
	3.3. In the groups being compared (exposed vs. non-exposed; with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups?				
	3.4. Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?				
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)?				
	4.2. Is the sample representative of the population understudy?				
	4.3. Are measurements appropriate (clear origin, or validity known, or standard instrument)?				
	4.4. Is there an acceptable response rate (60% or above)?				
5. Mixed methods	5.1. Is the mixed methods research design relevant to address the qualitative and quantitative research questions (or objectives), or the qualitative and quantitative aspects of the mixed methods question (or objective)?				
	5.2. Is the integration of qualitative and quantitative data (or results*) relevant to address the research question (objective)?				
	5.3. Is appropriate consideration given to the limitations associated with this integration, e.g., the divergence of qualitative and quantitative data (or results*) in a triangulation design?				
	<i>Criteria for the qualitative component (1.1 to 1.4), and appropriate criteria for the quantitative component (2.1 to 2.4, or 3.1 to 3.4, or 4.1 to 4.4), must be also applied.</i>				

*These two items are not considered as double-barreled items since in mixed methods research, (1) there may be research questions (quantitative research) or research objectives (qualitative research), and (2) data may be integrated, and/or qualitative findings and quantitative results can be integrated.

Appendix 2 Thematic synthesis: example of study summary

Title: Understanding and challenges in taking tyrosine kinase inhibitors among Malaysian chronic myeloid leukaemia patients: a qualitative study

Authors: Lim, Eng and Chan

Year: 2017

Journal: Asian Pacific Journal of Cancer Prevention

Study design

Research question/aim: “To explore their (patients’) understanding and challenges in taking both drugs (imatinib and nilotinib) which could eventually affect their adherence and thereby treatment outcomes”

Theoretical approach: Not reported

Context and participants

Study setting: A counselling room adjacent to the hospital pharmacy at the Sultanah Bahiyah Hospital, a “public tertiary care centre” which provides medical services for 2.1 million people in Northern Malaysia.

Population/location: 52 CML patients, taking imatinib or nilotinib, cared for by the haematology clinic at the above hospital.

Recruitment method (purposive sampling etc) and by who: List of CML patients who met inclusion criteria obtained from electronic hospital system. CML patients “purposively sampled” by one of the investigators, a pharmacist. Approached at pharmacy and briefed on study. Recruitment continued, “until data saturation was achieved”

Inclusions: Confirmed CML diagnosis, receiving follow up from haem clinic during the study period, and taking imatinib or nilotinib for at least 3 months.

Exclusions: Patients with hearing or cognitive impairment and those unable to communicate in Malay.

How many participants: “13 eligible patients were identified and agreed to participate in this study”

Participant characteristics (gender, age etc): Male = 8, Malay in origin = 10, Mean age = 47.8, tertiary education = 8, Imatinib = 9 nilotinib = 4, average treatment time = 2.6 years.

Study methods used

Data collection method: Each participant completed a self-administered questionnaire on sociodemographic characteristics including: gender, age ethnicity, educational level. Clinical treatment details: TKI type, duration and no of other medications obtained from the computer system. The patients interviewed by “one of the investigators”, taking 30-45 mins. “A semi-structured questionnaire was used to guide the interviews” (based on existing literature): 7 questions around knowledge of disease, treatment and monitoring, side-effects and how they are dealt with, non-adherence and anything else the patient wanted to discuss.

When were data collected: Study period 01/03/2016 – 31/05/2016.

Data analysis method

Method and process of analysis (thematic analysis, framework etc): No reported use of theoretical model to analyse data. Interviews transcribed compared with notes. Transcripts translated into English by 2 of the bilingual researchers (validated by another “research officer”)

Two of the investigators analysed the interviews independently using content analysis and constant comparison “was made between interviews”. “The themes, subthemes and quotes selected...were agreed by all the investigators”

Findings

Theoretical model used to interpret or contextualise the findings: None reported

Key themes/findings relevant to this review: Two main themes and 9 sub themes:

- Understanding about disease and treatment

Understanding about CML: Most understood a cancer of white blood cells and needed frequent blood tests. “Physical discomfort” and bleeding main CML symptoms. “Natural history and staging” of CML less well understood.

Understanding about TKIs: Poor level understanding about TKIs but high level confidence in treatment, relationship with physician important to this confidence.

- Challenges in taking TKIs

Adverse effects of TKIs: several side-effects reported, mostly “mild and tolerable” but did effect daily life significantly. Some SEs lead pts to skip TKI, some pts believed minor ailments e.g. cold, to be related to TKIs so adjusted dose, without consulting physician. Most pts chose to “ignore” the SEs and carried on with treatment and used “self-designed coping strategies”. All of those who switched from imatinib to nilotinib thought nilotinib was better and caused less sever N+V.

Forgetfulness: Several pts occasionally missed meds, all of whom said they took it as soon as they remembered, one talked about the importance of family to prompt meds.

Travelling: Many missed meds when travelling, particularly when unexpectedly delayed in another country, others didn't as took extra meds with them.

Religious and social issues: Muslim patients frequently missed doses during Ramadan. Attending meals with friends made taking nilotinib difficult.

Poor palatability and large tablet size: Several patients reported this.

Poor appetite: One patient missed due to GI SEs if not taken with food.

Concern over switching to a new TKI: One patient declined to switch to nilotinib due to more complicated regime.

Evidence gaps and/or recommendations for future research: None reported.

Source of funding: “No specific grant” received.

Appendix 3 Thematic synthesis: final coding frame under headings

MANAGING DISEASE AND MEDICATION

Distress at diagnosis

Unintentional non-adherence

Intentional non-adherence

Attitude to missing medication

Compensating for missed medication

Adherence motivation/belief

Adherence strategies

Non adherent behaviour change over time

Side-effects types

Managing SEs with help/independently

Availability of drugs

Switching TKI

CAM and spiritual medicine

Possible improvements: Consultation: HCP practice

Possible improvements: Consultation: HCP communication

Possible improvements: Resources: people

Possible improvements: Resources: facilities

Possible improvements: Resources: cost

Possible improvements: Adherence measurement

HCP ADVICE AND COMMUNICATION

HCP positive adherence advice

HCP negative adherence advice

Lack of HCP advice

Lack of HCP awareness

Reporting of issues to HCP

Non-reporting of issues to HCP

Facilitators to patient reporting

HCP/patient relationship/communication

PATIENT AWARENESS AND UNDERSTANDING

Some/good disease awareness

Lack of disease awareness

Need for information minimal

Reliant on Dr for information

Self-directed in seeking monitoring information

QUALITY OF LIFE

CML impact

Adapting to/coping with CML

Anxieties

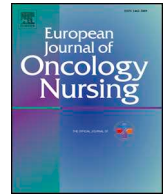
PATIENT PERSPECTIVE AND HOPES

Positive perspective

Negative/ambivalent perspective

Hopes for the future

Appendix 4 Publication of thematic synthesis



Experiences of living with chronic myeloid leukaemia and adhering to tyrosine kinase inhibitors: A thematic synthesis of qualitative studies

Ann Hewison*, Karl Atkin, Dorothy McCaughan, Eve Roman, Alex Smith, Graeme Smith, Debra Howell

ARTICLE INFO

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Adherence
Chronic cancer
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ABSTRACT

Purpose: To investigate the experiences of adults living with chronic myeloid leukaemia and treated with tyrosine kinase inhibitors, with particular reference to factors influencing adherence.

Methods: A thematic synthesis of all published qualitative studies examining adults with chronic myeloid leukaemia, receiving tyrosine kinase inhibitors. Eligible publications were identified by searching five electronic databases using defined criteria. The synthesis involved complete coding of extracted data and inductive theme development.

Results: Nine studies were included and three overarching themes defined. Overarching themes were: 1) Disease impacts whole life; 2) Disease management strategies; and 3) Valued aspects of care. Side-effects often required physical and psychological adaptation. Patients developed individual decision-making processes to promote adherence and manage side effects. Unintentional non-adherence occurred due to forgetfulness and system failures. Intentional omission also occurred, which together with side effects, was unlikely to be reported to healthcare professionals (HCPs). HCP reassurance about missed doses could reinforce non-adherence. Information needs varied over time and between individuals. Knowledge among patients about treatment was often lacking and could lead to misunderstandings. Patients valued psychological support from HCPs and suggested an individualised approach, facilitating discussion of symptoms, adherence and their perspectives about living with chronic myeloid leukaemia, would improve care.

Conclusions: Patients with chronic myeloid leukaemia experienced significant side-effects from treatment and changes to their psychological and physical well-being. They developed their own strategies to manage their disease and treatment. This should be recognised in interventions to improve education, support and the delivery of care that is compassionate and adequately resourced.

1. Introduction

Chronic myeloid leukaemia (CML) is a haematological malignancy arising when bone marrow stem cells produce excessive and abnormal white cells. Most people with CML have the Philadelphia chromosome which carries the defective *BCR-ABL1* gene, enabling production of a tyrosine kinase enzyme which stimulates the disease process (Frazer et al., 2007). It is characterised by a chronic, accelerated and blast phase, with most diagnoses made in the chronic phase and commonly associated with anaemia and splenomegaly (Jabbour and Kantarjian, 2018). A rare disease (European incidence 1–2/100,000 population), with an average age at diagnosis of around 57 years, CML is more common in men than women (Brunner et al., 2013; Pulte et al., 2013; Rohrbacher and Hasford, 2009; Smith et al., 2011; Visser et al., 2012). Incidence of CML does not differ by ethnic origin, geographical region

or socioeconomic status (Hehlmann et al., 2007; Smith et al., 2011).

The introduction of oral tyrosine kinase inhibitors (TKIs: targeted therapies given orally to block cancer cell growth) at the turn of the current century transformed CML from a rapidly fatal disease, to an illness with a chronic trajectory. Imatinib (or Gleevec/Glivec) was the first TKI to be introduced, followed by a range of 'second generation' drugs. Survival has since improved to the extent that European rates are now similar to those of the general population (Björkholm et al., 2011; Smith et al., 2014). Response to TKIs is described as "the most important prognostic factor" for CML management in the European LeukaemiaNet recommendations (Baccarani et al., 2013) and has the greatest effect on survival. Importantly, several studies examining treatment have identified a link between adherence and response (Almeida et al., 2013; Ganesan et al., 2011; Marin et al., 2010; Noens et al., 2009), with influencing factors including: drug dose, time since

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diagnosis, treatment duration, comorbidity, clinician/patient relationships and patient understanding of CML (Gater et al., 2012; Noens et al., 2014). Since more people are living with the long-term effects of CML (Atallah and Ritchie, 2018), health related quality of life (HRQOL) and symptom burden have gained particular importance. Unfortunately, however, significantly worse outcomes are reported in people with CML compared to the general population (Efficace et al., 2011; Phillips et al., 2013); a situation which can affect adherence (Marin et al., 2010).

Research examining these issues has been criticised for taking a “reductionist biomedical” approach, measuring only objective predictors of non-adherence (i.e. disease and treatment related factors), rather than investigating the role of patients’ beliefs, experiences and social situation (Gater et al., 2012). As Sabaté (2003) highlight in their key World Health Organisation (WHO) report, viewing the patient as having individual responsibility for adherence ignores contextual factors which impact upon it, such as socioeconomic and health system issues. More recently, however, qualitative studies have examined broader patient experiences (e.g. Graffigna et al., 2017; Lim et al., 2017). The pragmatic aims of the current study are to: 1) explore how individuals perceive and describe their experiences of taking long-term TKIs, with particular reference to adherence, side effects and quality of life; and 2) generate evidence that can be used to guide clinical practice.

2. Methods

Although the first part of the synthesis is an open question (to explore the CML experience), suggesting iterative or interpretive approaches were appropriate (Barnett-Page and Thomas, 2009; Dixon-Woods et al., 2006, 2005; Paterson, 2012), the second part (to inform clinical practice) is more pragmatic. Various methods of qualitative synthesis were investigated to find a methodological approach that could incorporate both aspects of the research question, with thematic synthesis considered the most appropriate. Thematic synthesis is a realist approach, which permits an open research question and also reflects our pragmatic aim. In this way, it is comparable to the idea of “subtle realism” (Hammersley, 1992), which accepts that there is a shared reality outside of us, but that one can only know this reality through the minds and perspectives of individuals. Other factors, such as researcher experience and background, available resources and type of data also suited the thematic synthesis approach. Methods were guided by key references (Braun and Clarke, 2013; Thomas and Harden, 2008), as recommended (Barnett-Page and Thomas, 2009; Booth et al., 2016; Flemming, 2007; Paterson, 2012), and are presented below in accordance with the ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) statement (Tong et al., 2012).

2.1. Search strategy, eligibility and screening

A systematic search of: “chronic myeloid leukaemia or chronic myeloid leukaemia or leukaemia myelogenous chronic BCR-ABL positive” and “patient satisfaction or patient experience or qualitative research” was conducted within MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index: Web of Science, and Google Scholar. Electronic alerts were set up in each site, with Scopus used to check citations. The initial search was conducted in 2016, with papers screened for eligibility (see Table 1 for criteria) using the study abstract or full text.

Initial data base searching and citation searches led to the identification of 104 studies, with 7 additional papers found via database alerts (up until September 2019). After the removal of duplicates, 100 studies were screened and 91 removed. Nine studies emerged as eligible, as shown in the PRISMA flow chart in Fig. 1 (Liberati et al., 2009). Table 2 provides summaries of the included studies. Strengths and limitations of eligible studies were appraised by two researchers (AH, DM) using a quality assessment tool (Hawker et al., 2002). Each study was examined using this tool (Hawker et al., 2002) to allocate gradings (‘poor’, ‘fair’ and ‘good’), as shown in Table 3. Strengths were

Table 1
Eligibility criteria.

	Inclusion	Exclusion
Participant characteristics	CML diagnosis Aged ≥ 18 years Males and females Chronic phase Long-term TKI use (i.e. lifelong) Outpatient management Any geographical location	Aged ≤ 18 years Accelerated/blast phase Receiving end-of-life care Not treated with TKIs Inpatient management
Type of study	Qualitative	Clinical trials/ quantitative Systematic reviews Non-English language

noted in the reporting of findings, which ranged from descriptive to conceptual accounts, with quotations being consistent and illustrative of results and themes. Weaknesses were noted in most studies: several did not describe the relationship between researchers and participants or inclusion/exclusion and sampling criteria; others used a theoretical framework but did not report how this was applied during data analysis.

2.2. Data extraction and coding

Extracted data included participant quotations, researcher summaries, and analytical concepts and interpretations, which ensured findings were captured clearly (Thomas and Harden, 2008). Thematic synthesis involved complete coding of extracted data, with codes derived inductively, based on the study aims (Braun and Clarke, 2013; Thomas and Harden, 2008). This was carried out manually (AH), with text highlighted and annotated prior to the generation of codes/sub-codes, named to encapsulate “meaning and content” (Thomas and Harden, 2008). Codes were compared across eligible publications, with new entities created and existing fields merged until a coding frame was finalized (Braun and Clarke, 2013). Publications and coding schemes were uploaded into NVIVO, which was used as a retrieval tool for theme development. Themes were developed inductively (AH), based on similarities and differences between codes, with figurative meaning sought via visual mapping and iterative checking, independently assessed by a second researcher (DM). Themes and sub-themes are reported in the Results, represented by patient quotations and excerpts from author-interpretations.

3. Results

Characteristics of the nine included studies are shown in Table 2. All were published 2011–2018 and included people receiving imatinib or second line TKIs for CML. Not all studies reported the type of TKI as follows: i) Imatinib: 4 studies; ii) TKI (type not reported): 3 studies; iii) “first and second line TKIs”: 1 study; iv) Imatinib or nilotinib: 1 study. Often the emphasis was on adherence, but studies also explored patient perceptions of CML, disease stage, disease impact and health-seeking behaviour. All publications contained patient interviews and one also included health care practitioners (HCPs) (Wu et al., 2015). Only data from the patient sample in the latter study was used in the synthesis, to comply with eligibility criteria. Studies were located in Europe, Africa, Australia and South East Asia; and used various qualitative methods, including ethnography, interpretative phenomenological analysis and grounded theory.

Thirty-eight codes were generated from included studies with three overarching themes: 1) Disease impacts whole life; 2) Disease management strategies; and 3) Valued aspects of care; each of which had multiple sub-themes. Themes and sub-themes are reported in the

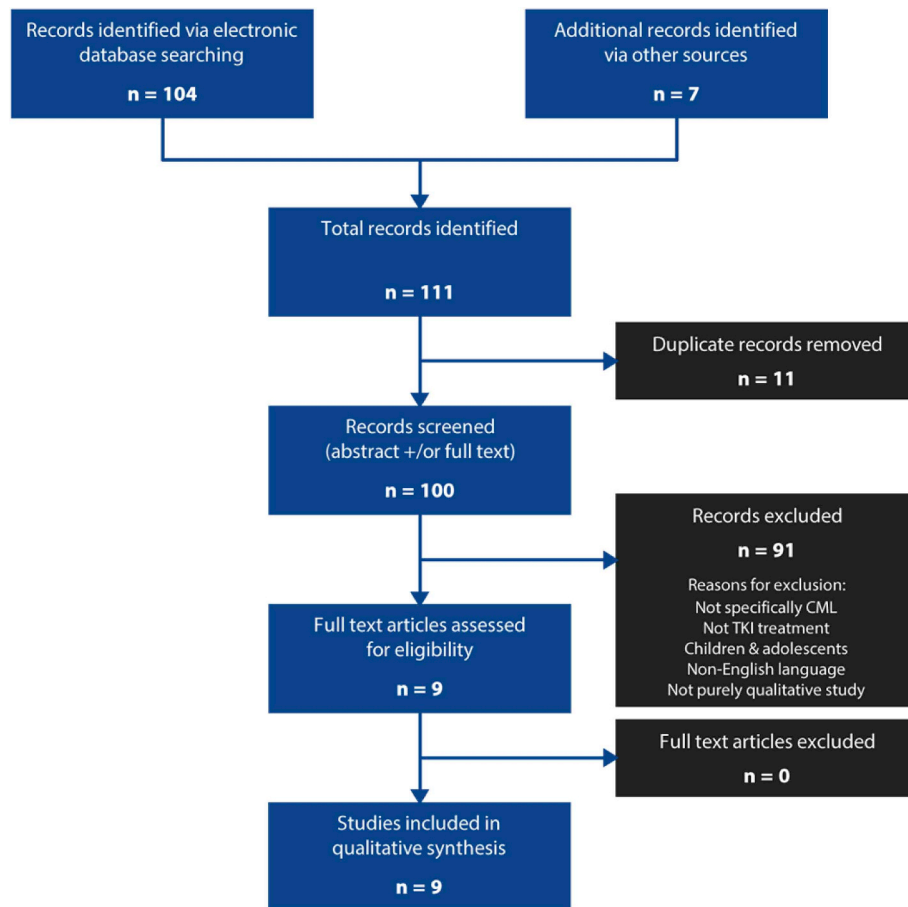


Fig. 1. Screening process and identification of eligible studies.

following section, with verbatim patient quotations and excerpts from author-interpretations, which are clearly marked as such. Themes are also summarised in Fig. 2, which demonstrates how the initial impact of a CML diagnosis influences the way individuals manage their disease and treatment at this time, and the effect of factors arising over the life-course, including hospital care, disease awareness and changing perspectives and beliefs. Overall, Fig. 2 illustrates the individual, situated within the context of what is essentially chronic cancer.

4. Theme 1: disease impacts on whole life

This theme relates to the physical, psychological and practical impacts of living with CML, including the effect of this cancer on different areas of life.

4.1. Side effects

Side effects from TKI treatment were common and reported as physical or psychological. Physical symptoms commonly included nausea and/or vomiting, pain, skin problems and fatigue. Medication and disease effects were reported as impacting on daily life, usual activities and adherence (Bolarinwa et al., 2018; Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Lim et al., 2017; Tan et al., 2017; Wu et al., 2015):

“Tiredness of colossal, you know—I’ve got a young family and just sort of trying to keep up with the daily routine of that is not easy.” (Wu et al., 2015, p258)

“... I don’t want to take it, because it makes me feel sick. And the next day I’d feel a bit better, because I’d not had themI consciously didn’t

take it. Because I didn’t want to take it ...” (Eliasson et al., 2011, p629)

Psychological effects included low mood, but also heightened general health awareness and changes in self-identity through a lessening of self-efficacy and the change from individual to patient (Chen et al., 2014; Graffigna et al., 2017; Guilhot et al., 2013):

“I was a young man at that stage, I was full of energy and enthusiasm. Full of projects for the future. I felt that I was unbeatable. The diagnosis initially destroyed me and my perceived strength” (Graffigna et al., 2017, p2748,)

Side effects could, however, be mild, or managed by switching to second generation TKIs (Bolarinwa et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Guilhot et al., 2013; Lim et al., 2017).

4.2. Adapting daily life

Many areas of life were affected by CML and its treatment; including employment, leisure activities and family roles (Bolarinwa et al., 2018; Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Graffigna et al., 2017; Guilhot et al., 2013; Lim et al., 2017; Wu et al., 2015). Practical concerns about employment and financial matters were reported by several patients, in relation to side effects of TKIs, the need for frequent hospital appointments or stigma relating to the disease (Chen et al., 2014; Graffigna et al., 2017; Guilhot et al., 2013; Tan et al., 2017) In response, patients adapted their routines to cope and manage, including changing work commitments and/or stopping hobbies (Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Graffigna et al., 2017; Guilhot et al., 2013):

“I can work 75%, and that is not a major issue in the sense that health is

Table 2
Summary of included studies.

Author/year	Population/country	Participants (N, age, sex)	Research question	Data collection	Research approach/analysis
Eliasson et al. (2011)	CML patients attending hospital, UK	N = 21 Age 33-70 Male 11, Female 10	To explore the experience of CML patients of taking (or not) imatinib as prescribed	In-depth unstructured interviews	Constant comparison
Guilhot et al. (2013)	CML patients from clinical centres and online communities, Brazil, France, Germany, Russia and Spain	N = 50 Age 21-80 Sex not reported	To assess the effects of diagnosis and treatment on patients with CML and offer recommendations for HCPs to better support patients	In-depth, semi-structured interviews with patients and relatives. Diary, photo journal and debriefing interview (Brazil and France only)	Ethnography
Chen et al. (2014)	CML patients attending an oncology outpatient clinic, Southern Taiwan	N = 42 Age 20-80 Male 23, Female 19	To explore CML patients' experiences of treatment with imatinib, and understand perceptions, attitudes and concerns that may influence adherence	Semi-structured interviews	Constant comparison; theme saturation
Wu et al. (2015)	CML patients and HCPs at a specialist cancer centre, Australia	Patients: N = 16 Age 26-71 Male 9, Female 7 Practitioners: N = 10 (4 Haematologists, 3 nurses, 3 pharmacists)	To explore and compare patient experiences with HCP perceptions of imatinib	Semi-structured interviews	Interpretative phenomenological analysis
Bolarinwa et al (2018)	CML patients attending the only hospital providing free imatinib, Nigeria	N = 20 Age 25-56 Male 10, Female 10	To evaluate delayed diagnosis, health-seeking behaviour, medication use and other challenges faced by people living with CML on imatinib	In-depth semi-structured interviews	Grounded theory (until saturation); content analysis of themes
Graffigna et al. (2017)	CML patients in 22 onco-haematological centres, Italy	N = 158 Characteristics not reported	To reconstruct the subjective meaning- process related to CML and explore the psychological impact of suspending therapy	Narrative diaries	Narrative inquiry. Lexicography software analysis and a "purely qualitative analysis" of narratives by hand.
Lim et al. (2017)	CML patients at a tertiary care centre, Northern Malaysia	N = 13 Age 47.8 (mean) Male 8, Female 5	To explore patients' understanding and challenges in taking imatinib and nilotinib	Semi-structured interviews Questionnaire	Content analysis
Boons et al. (2018)	CML patients from a Dutch advocacy group, treated at 9 hospitals, Holland	N = 13 Age 27-73 Male 5, Female 8	To understand reasons for non-adherence and patient need for information and communication	Semi-structured interviews Questionnaire	Mixed methods Qualitative thematic framework analysis

Table 3
Quality appraisal of included articles using Hawker et al. (2002).

Author/year	Abstract/title	Introduction/aims	Methods/data	Sampling	Data analysis	Ethics/bias	Findings	Transferability/generalisability	Implications/usefulness
Eliasson et al. (2011)	Good	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair
Guilhot et al. (2013)	Good	Fair	Good	Fair	Fair	Fair	Good	Fair	Fair
Chen et al. (2014)	Good	Fair	Fair	Fair	Poor	Fair	Fair	Fair	Fair
Wu et al. (2015)	Fair	Good	Fair	Fair	Fair	Fair	Fair	Fair	Good
Bolarinwa et al. (2018)	Fair	Fair	Fair	Fair	Poor	Fair	Good	Fair	Fair
Graffigna et al. (2017)	Fair	Fair	Fair	Poor	Fair	Poor	Fair	Poor	Fair
Lim et al. (2017)	Good	Good	Good	Fair	Poor	Fair	Fair	Good	Good
Tan et al. (2017)	Good	Good	Good	Fair	Fair	Fair	Good	Fair	Good
Boons et al. (2018)	Fair	Fair	Fair	Fair	Poor	Fair	Good	Fair	Good

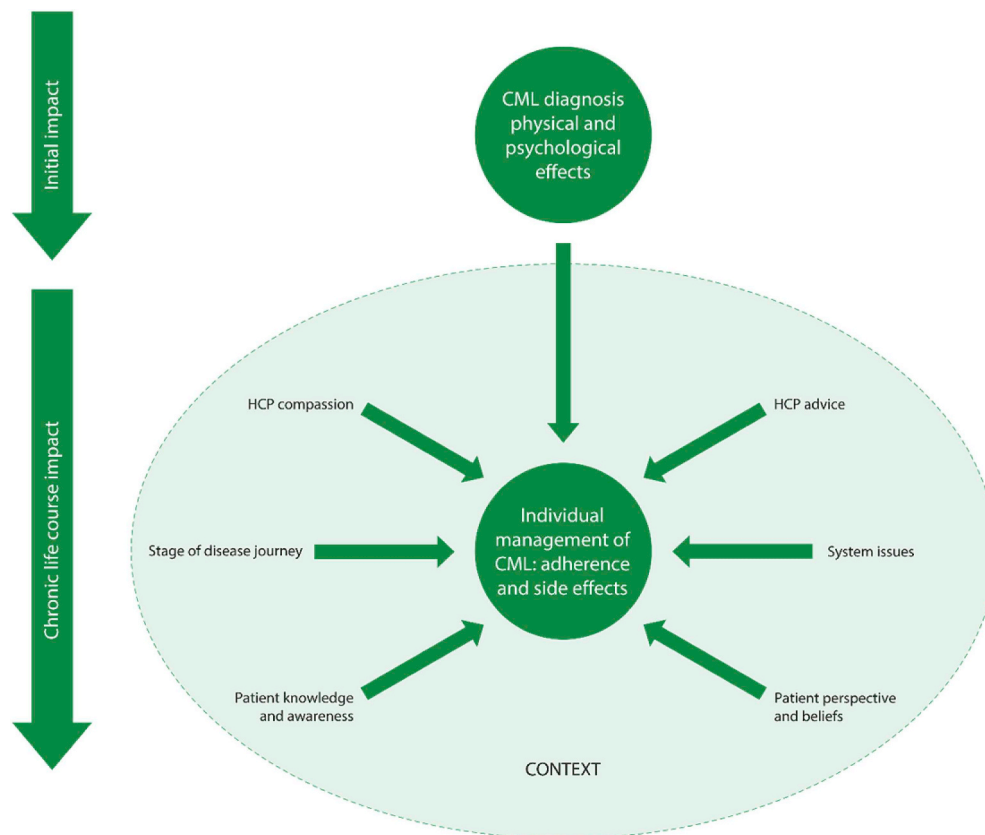


Fig. 2. The patient experience of CML in context and over time.

more important, but it has a major impact on my life” (Boons et al., 2018, p647)

Conversely, living with CML was reported as having little impact on daily life by fewer patients, often after treatment had started (Chen et al., 2014; Guilhot et al., 2013; Lim et al., 2017). Patients also described how their disease and treatment affected family and friends and how they perceived the practical and psychological support from these groups as vital (Graffigna et al., 2017):

“My family was badly affected by my disease. They were shocked at first, but as time went by they became such an important support for me.” (Graffigna et al., 2017, p. 2747)

4.3. Changing perspectives

Only two publications referred to the ‘patient journey’ (Graffigna

et al., 2017; Guilhot et al., 2013), although all noted changing perspectives according to time since diagnosis. The early post-diagnostic period was defined by ‘shock’, ‘anxious alert’ (described as a heightened awareness of their health) or ‘crisis’, with some patients saying they felt pessimistic and fearful (Graffigna et al., 2017; Guilhot et al., 2013):

“I hyper-scrutinized my body in search of new symptoms or signals that my health was worsening. At that stage I was certain that ‘the worst’ was still to come.” (Graffigna et al., 2017, p2749,)

This was followed by a process of adaptation, involving the dissipation of anxious feelings, before disease/treatment acceptance (Bolarinwa et al., 2018; Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Graffigna et al., 2017; Guilhot et al., 2013; Lim et al., 2017; Wu et al., 2015). Adaptation was an active process, involving growing knowledge and understanding of disease, increased awareness of blood results showing treatment response, and activity adjustments:

"It was all about the children before, educating and dressing them ... Now I pay attention to myself more. I listen to myself and to what my body says." (Guilhot et al., 2013, p89)

One study reported patients finding it easier to talk about their disease once they had reached acceptance, with people diagnosed more recently saying they found adaptation easier, possibly due to the availability of effective treatments, with better prognosis (Guilhot et al., 2013). Some patients said they had gained more positive perspectives and felt 'lucky' they had CML rather than a more acute cancer (Bolarinwa et al., 2018; Graffigna et al., 2017; Guilhot et al., 2013; Wu et al., 2015):

"There's a lot more people worse off than me so [I] don't complain too much." (Wu et al., 2015, p259)

Judging themselves as more fortunate was described as 'downward comparison' and was thought to lead to reluctance among some patients to seek help from HCPs (e.g. for side effects), (Wu et al., 2015). In contrast, patients also reported continuing feelings of fear and sadness:

"I think I've adjusted to CML. Although to be honest I have to say that I still sometimes feel sad." (Graffigna et al., 2017, p2749)

Some patients developed a more negative perspective over time due to their experience of side effects:

"In the course of time of treatment, patients developed more negative beliefs about TKI due to side effects (e.g. "nasty pills, "a drama")" (Boons et al., 2018, p648, author quotation).

As patients achieved a 'new normal' (Guilhot et al., 2013) following acceptance and adaptation, they were said to renew life plans, such as marriage, friendships and hobbies (Graffigna et al., 2017; Guilhot et al., 2013). Patients expressed feelings which were optimistic, such as hoping to stop treatment in due time (Boons et al., 2018; Graffigna et al., 2017; Wu et al., 2015), but also feelings of fear for the future (Boons et al., 2018; Chen et al., 2014; Graffigna et al., 2017; Guilhot et al., 2013):

"The idea of no longer responding is worrisome and you wonder about it when you have a chronic disease." (Guilhot et al., 2013, p90)

5. Theme 2: disease management strategies

This theme captures patient behaviour (disease management and awareness, adherence, management of side effects), at an individual level and in the context of external influences, such as practitioner advice and drug availability.

5.1. Patients have their own management strategies

Patients described many strategies used to help them take their TKI medication, including routine/forward planning, often with family support (Bolarinwa et al., 2018; Boons et al., 2018; Eliasson et al., 2011; Guilhot et al., 2013; Lim et al., 2017; Wu et al., 2015):

"My husband reminds me to take my drug; at times my phone ring[s] when it gets to the time to take it, I have never missed it ..." (Bolarinwa et al., 2018, p198)

Patients also developed various techniques to manage symptoms/side effects, such as taking medication around mealtimes or before going to bed, to reduce the effects of nausea (Chen et al., 2014; Eliasson et al., 2011; Lim et al., 2017; Wu et al., 2015):

"I changed to take the medicine before bed-time or after a meal. If I take it with an empty stomach, I will definitely vomit it out in ten minutes." (Chen et al., 2014, p124)

However, whilst data suggest some patients were willing to consult

HCPs about disease related issues, such as stopping medication, the opposite appeared more common regarding side effects or adherence (Eliasson et al., 2011; Lim et al., 2017; Wu et al., 2015); meaning that HCPs could be unaware of difficulties. Reasons given by patients for non-consultation included reluctance to bother HCPs and/or patients considering their symptoms trivial. Similarly, patients were unlikely to inform HCPs about missed medication, thinking it was not important, not wanting to upset their doctor, or they could judge themselves whether a consultation was required (Eliasson et al., 2011; Lim et al., 2017; Wu et al., 2015):

"I forgot to take the medicine with me. I'm a little bit worried, but I say no it's too late now and I don't want to tell the doctor, I don't want to upset the doctor". (Wu et al. p.258)

"I was unable to hear for about a week, so I self-adjusted the dose I did not seek the consultation from doctors because my next clinic visit was 3 months after that." (Lim et al., 2017, p1927)

Some patients reported using complementary and alternative medicines to deal with side effects or for general health, such as herbal preparations and vitamin supplements (Bolarinwa et al., 2018; Wu et al., 2015). Such medicines were also sometimes used as an alternative to TKIs for those who held a strong belief in traditional medicine or when specialist care coverage was inadequate, causing a delay in diagnosis or interruption in TKI treatment (Bolarinwa et al., 2018; Tan et al., 2017):

"I was very ill, I could not stand and I have no blood that my husband took me to several hospitals and herbalist homes with no relief." (Bolarinwa et al., 2018, p197)

5.2. Patients make their own decisions about adherence

Some patients occasionally decided to omit their TKI medication intentionally, often to avoid side effects. This enabled them, for example, to eat and drink normally on social/religious occasions or during periods of illness, which could be further complicated by medication that involved fasting prior to administration (Bolarinwa et al., 2018; Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Lim et al., 2017; Tan et al., 2017; Wu et al., 2015):

"... I thought there was no way I was going [on holiday] and being tired. So I did actually stop taking the tablets for a week before I went ..." (Eliasson et al., 2011, p629)

Some reported feeling better after missing TKI medication, as side effects were absent (Eliasson et al., 2011). Unintentional non-adherence was also reported, commonly due to simple forgetfulness, often caused by a change in routine, travelling or social occasions (Bolarinwa et al., 2018; Boons et al., 2018; Eliasson et al., 2011; Graffigna et al., 2017; Lim et al., 2017; Tan et al., 2017; Wu et al., 2015):

"My drug is my life, I try to follow the dosage on the doctor's prescription, but it might sometimes happen that I forget." (Graffigna et al., 2017, p2746)

Patients' beliefs about their medication affected motivation to adhere (Bolarinwa et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Lim et al., 2017; Wu et al., 2015). Some reported fear of progression, others described themselves as 'conformists' who strictly followed medical advice, or said they had 'faith' in their doctor and treatment (Eliasson et al., 2011; Wu et al., 2015):

"... It's a belief really, that's keeping me going. I've now put all my faith in [the imatinib]. From day one I've got faith in [my clinician]." (Eliasson et al., 2011, p629)

Beliefs and misunderstandings about TKI medication could also result in non-adherence; for example, a fear of long-term effects or

believing TKIs are only required if symptomatic (Chen et al., 2014; Tan et al., 2017):

"I'm not sure about taking this medication, I feel well." (Tan et al., 2017, p1031)

Whilst some patients adhered because they did not experience side effects, others did so despite side effects (Eliasson et al., 2011). Data from one publication suggests adherence can change over time (Eliasson et al., 2011) being initially poor as individuals 'got used to' the medication, or decreasing over time, as motivation to adhere decreased, and response to medication had been achieved.

When faced with the decision of how to compensate for missed medication, some said they always took their treatment as soon as they remembered (usually the same day), whilst others reported not taking missed dose(s). Reasons patients did not compensate for missed doses included: thinking the missed dose would not affect response; feeling they could judge for themselves whether to change doses; not wanting to bother their doctor; or simply being unable to remember if they had taken a tablet or not (Boons et al., 2018; Eliasson et al., 2011; Lim et al., 2017; Tan et al., 2017; Wu et al., 2015)"

"I get into the car, due to take off and remember about that, and I say, 'Ah, only one day'; don't worry about that." (Wu et al., 2015, p258)

5.3. External influences on disease management

Decisions about adherence were made within the context of health and social systems. Unintentional non-adherence could also be due to prescription errors, difficulties with pharmacy (Eliasson et al., 2011) or problems accessing medication, and in certain countries (Nigeria and Malaysia), the costs of disease monitoring (Bolarinwa et al., 2018; Tan et al., 2017). Communication issues were cited as a barrier to TKI adherence, with some patients unable to gain access to advice (Eliasson et al., 2011; Wu et al., 2015):

"...I guess because you don't want to get told off for not taking it, you know. And [if I take my imatinib or not] is not something I've been specifically asked either." (Eliasson et al., 2011, p629)

In some countries (e.g. Nigeria, Malaysia, Brazil and Russia), a limited supply of TKIs or out of pocket costs, such as laboratory costs and long journeys to hospital appointments, could affect adherence (Bolarinwa et al., 2018; Guilhot et al., 2013; Tan et al., 2017):

"Before [this] my blood test BCR-ABL is free, now I need to pay hundred [s] over. For private [care], we struggle" (Tan et al., 2017, p1032)

Although the synthesis indicated that high levels of adherence are encouraged by HCPs, there is also evidence that HCPs may unintentionally reinforce non-adherence by reassuring patients that "missing the odd dose" is acceptable (Bolarinwa et al., 2018; Eliasson et al., 2011; Wu et al., 2015):

"I've missed a couple of nights and I've rang like the research nurse and she said, 'Look, don't stress. It's only one night'." (Wu et al., 2015, p260)

Patients may also interpret 'stable response' to mean missing medication is safe (Bolarinwa et al., 2018; Boons et al., 2018; Eliasson et al., 2011):

"Some patients perceived that the missed dose would have no effect on their TKI response and they argued that their haematologist also sometimes said to stop treatment for a period when experiencing side effects ..." (Boons et al., 2018, p648, author quotation)

The extent to which support was provided around adherence and

the management of side effects differed between publications (Bolarinwa et al., 2018; Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Guilhot et al., 2013; Wu et al., 2015); and as already noted, conflicting advice could be given about missing medication (Eliasson et al., 2011; Wu et al., 2015):

"Twelve out of 21 patients made comments in relation to receiving feedback that seemed to have reinforced the belief that 'occasional' non-adherence did not matter." (Eliasson et al., 2011, p628, author quotation)

Some data suggest that lack of awareness among HCPs about the extent of non-adherence could be due to their reliance on blood-monitoring rather than asking patients (Eliasson et al., 2011; Wu et al., 2015). Patients also said little advice was provided about if/how to compensate for missed medication and often made this decision themselves (Eliasson et al., 2011; Lim et al., 2017; Wu et al., 2015). Patients also indicated that advice on managing side effects could also be lacking (Boons et al., 2018; Wu et al., 2015):

"When I vomited, the information wasn't there; do I take another dose, don't I, will I overdose?" (Wu et al., 2015, p260)

5.4. Varying patient knowledge and information needs over time

Patient knowledge and understanding was said to influence disease management, including side effects, adherence and reporting to HCPs (Chen et al., 2014; Eliasson et al., 2011; Graffigna et al., 2017; Lim et al., 2017; Wu et al., 2015). Some patients showed awareness about CML. More, however, lacked knowledge, particularly about treatment (Boons et al., 2018; Chen et al., 2014; Eliasson et al., 2011; Lim et al., 2017; Wu et al., 2015). Misunderstandings included thinking medication was 'stored' in the body (Wu et al., 2015), being unclear on indicators of progression and not fully understanding monitoring:

"... the nurse insisted that I need to have a regular check, that's strange, I can't see why it's necessary." (Chen et al., 2014, p123)

Some patients wanted HCPs to interpret their blood results (Guilhot et al., 2013; Wu et al., 2015), while others preferred to be involved themselves:

"I get the results personally, read them first, and bring them to my doctor." (Guilhot et al., 2013, p85)

Boons et al. (2018) reported that patients expressed a need for information to be current and presented in an honest, understandable format, including written material. There was a particular need for more information on side effects, including impact on sexuality. Patients also wanted more information about hospital appointment systems and social support:

"It should be honest, I want to know exactly what to expect" (Boons et al., 2018, p647)

Guilhot et al. (2013) described patient need for information at each stage in the 'CML journey', saying only basic disease/treatment understanding was needed during the initial 'crisis'/'shock' phase; with more detail required during 'adaptation'. Disappointment amongst patients was noted, concerning how little information clinicians offered at this time:

"Patients said that their HCPs provided little to no guidance on how to properly take their therapy and that they implemented their own methods to standardize their drug-taking routines." (Guilhot et al., 2013, p88, author quotation)

Upon reaching the 'new normal', patients' anxieties reduced and the

need for information was said to be minimal (Guilhot et al., 2013).

6. Theme 3: valued aspects of care

This theme describes factors valued by people with CML about their care, and potential improvements suggested by patients and HCPs.

6.1. Factors valued by patients and HCPs

Importantly, rather than education, patients appeared to place greater value on psychological support, offered by HCPs who were accessible, had a caring attitude and would provide reassurance (Bolarinwa et al., 2018; Boons et al., 2018; Eliasson et al., 2011; Guilhot et al., 2013; Lim et al., 2017). The importance of trust and 'faith' in HCPs was also discussed (Eliasson et al., 2011; Guilhot et al., 2013; Lim et al., 2017):

"I was shocked when I was first diagnosed with this disease, but my doctor gave me encouragement. He assured me that this medication will help me, so I felt more relaxed." (Lim et al., 2017, p1927)

"my doctor make[s] sure I get it even during doctor's strike, he also calls me to find out how I am doing." (Bolarinwa et al., 2018, p197)

"I feel that I am in very good hands. I trust my doctor fully." (Guilhot et al., 2013, p85)

Interestingly, more recently diagnosed CML was described by some patients and their HCPs as 'low key', in that it was a chronic disease, treatable with low-intensity oral medication. (Chen et al., 2014; Guilhot et al., 2013; Wu et al., 2015):

"Another patient was "happy knowing there's a pill [she] can pop" (PT7), noting that other potential treatments were associated with reduced efficacy or greater toxicity." (Wu et al., 2015, p259)

"The first doctor ... said that it was leukemia but I should not be worried because medicine is very developed nowadays," (Guilhot et al., 2013, p88, p88)

Whilst this depiction of CML could alleviate anxiety for some, it could also suggest to patients that they should be able to manage their CML themselves, thus contributing to disinclination to consult HCPs.

"I can judge it by myself, as I know my condition very well. If I have a flu or fever, I will reduce the dose by myself." (Lim et al., 2017, p1927)

6.2. Interpersonal and resource-based improvements in care

Several papers suggested patient/HCP consultations could be more open and individualised (Eliasson et al., 2011; Graffigna et al., 2017; Wu et al., 2015), with better advice on TKI treatment options (Chen et al., 2014; Guilhot et al., 2013), managing side effects (Boons et al., 2018; Guilhot et al., 2013; Lim et al., 2017), dealing with omitted doses (Chen et al., 2014; Eliasson et al., 2011; Wu et al., 2015), monitoring response (Guilhot et al., 2013) and establishing drug-taking routines (Eliasson et al., 2011; Guilhot et al., 2013; Tan et al., 2017). Supportive, non-judgemental and open dialogue, taking account of the patient's personal 'narrative', was also recommended to encourage the sharing of anxieties and adherence behaviour. This reflected patients' accounts of what they value in their HCP:

"... open communication will be beneficial to the patient in the management of CML throughout his or her journey." (Guilhot et al., 2013, p91, author quotation)

Regarding resources, data indicated that input was lacking from community services, with patients saying their General Practitioner (GP) and local pharmacists had little knowledge of CML (Eliasson et al., Wu et al., 2015). Suggested improvements included more clinic staff

and training people with CML as 'counsellors' for other patients, (Bolarinwa et al., 2018). With respect to facilities and costs, longer-term prescriptions were suggested by both patients and HCPs (Chen et al., 2014):

"a two-week schedule just passes too quickly, we should be allowed to have a long-term drug supply and only come to visit the doctor when we don't feel right." (Chen et al., 2014, p124)

7. Discussion

The nine qualitative studies included in this thematic synthesis clearly show that CML can have a significant impact on physical and psychological well-being and daily activities. TKI treatment side effects, traditionally physician assessed and reported as mild to moderate in clinical trials (Baccarani et al., 2014; Efficace and Cannella, 2016; Flynn and Atallah, 2016), were found to be widespread and disruptive. Interestingly, within work to develop and test CML specific patient reported outcomes measures, other authors report that the majority of patients with CML experienced persistent symptoms, ranging from mild to severe (Williams et al., 2013; Zulbaran-Rojas et al., 2018). It has been suggested that such long-term symptom burden may be more difficult to tolerate than intensive treatment, given short-term with curative intent (Frick et al., 2017). As previously noted, living with CML is also related to significantly worse health related quality of life (HRQOL) (Efficace et al., 2013; Williams et al., 2013; Zulbaran-Rojas et al., 2018), than found in the general population (Efficace et al., 2011; Phillips et al., 2013). In response, validated CML specific HRQOL and symptom burden questionnaires have been developed (Efficace et al., 2014; Williams et al., 2013), signifying a move away from physician assessed side-effects to patient reported outcome measures.

Our synthesis highlights the chronicity of CML and evidences patients gradually developing strategies, beliefs and decision-making processes to manage their disease, adherence and side effects; often without consultation with hospital clinicians and sometimes without a thorough understanding of their treatment. This is potentially relevant to other cancers managed with oral medication, which represents around 25% of all current cancer treatments in the United States of America (USA) (Abbott et al., 2014; Weingart et al., 2008). This shift from hospital based intravenous therapy to self-managed home treatment has many similarities with chronic illnesses, such as diabetes and cardiovascular diseases, which also tend to be self-managed.

Aspects of self-management in chronic illness, such as adherence to medication are widely documented (Velde et al., 2019). The multifactorial nature of non-adherence to medication in chronic disease as a global burden has been well described in a key WHO report (Sabaté, 2003) and consequent literature. Less well documented are definitions of chronic cancer and patient experiences of chronic cancer, including their disease management and hospital care (Harley et al., 2019; Pizzoli et al., 2019). Interestingly, patient reluctance to seek clinician advice regarding non-adherence and side effects identified in the current study, is corroborated in one of few studies on chronic cancer experience (Harley et al., 2019), and a large survey highlighting unmet needs among CML patients (Breccia et al., 2015).

Our study provides insight and understanding into the complexities CML patients face, contributing context to what is already known. It highlights how patients may lack knowledge about treatment; change their perspective on life; and the influence of HCPs in terms of the way they deliver care and advice. Regarding healthcare systems, it describes the possibility of hospital errors, pharmacy delay and blood monitoring issues. Other authors suggest further complexity due to adherence being underpinned by several factors, including side effects, co-morbidities and physician characteristics (Darkow et al., 2007; Marin et al., 2010; Noens et al., 2009). The multifactorial nature of chronic cancer symptoms is also said to contribute (Frick et al., 2017; Zulbaran-Rojas et al., 2018) with fatigue, for example, not only relating to treatment, but also

psychological distress, physical side effects (e.g. pain), and the impact of these on daily life (e.g. ability to work) (Efficace et al., 2013; Hofman et al., 2007; Zulbaran-Rojas et al., 2018).

Additional complexity is introduced by HCPs if they inadvertently provide conflicting or misguided advice to patients; are unaware how individuals cope with treatment and side effects; or do not provide sufficient or consistent psychological support. Wu et al. (2015) highlight complexity of care delivery from the perspective of HCPs, with issues such as budget and time restraints preventing adequate support, and language issues and miscommunication between hospital departments effecting adherence. This study also reports alignment between HCPs and patients regarding the late identification of side effects and perceptions of CML as a low maintenance disease. In recognition of such complicated pathways and experiences, and the impact of health system factors, Harley et al. (2019) developed the Chronic Cancer Experience Questionnaire (CCEQ), which includes multidimensional questions on side effects and daily activities, but also psychological wellbeing and the use of clinical services and available support.

Given the complexity of CML, its increasing prevalence in the TKI era, and emerging evidence of unmet needs, it is important that adequate care and support is available during long-term survivorship. Although this phase is well documented (Department of Health, 2013; Mayer et al., 2014; McCabe et al., 2013), much available literature refers to the time-period 'beyond' treatment, with little addressing experiences of 'living with' chronic cancers whilst taking continual oral medication, as occurs with CML. This concurs with results from a study in the USA (Frick et al., 2017), where fewer survivorship care plans were reported for patients with chronic cancer (including CML), than for those treated with curative intent.

Although a review of haematology survivorship models identified a diverse range of programmes and suggested primary care HCP involvement (rather than haematology alone or another single discipline), the models were said to lack measures of effectiveness (Taylor et al., 2015). Unclear professional responsibilities, lack of skills and educational resources, and (concurrent with this synthesis), insufficient time, have all been identified as barriers to nurses providing adequate care during survivorship for patients with haematological malignancies (Langbecker et al., 2016; Wallace et al., 2015). Unfortunately, this is associated with a lack of studies addressing self-management interventions for cancer patients in general (Howell et al., 2019), despite considerable literature focusing on factors effecting self-management and the impact of such interventions in chronic disease (McBain et al., 2015; Schulman-Green et al., 2016; Vassilev et al., 2011).

This is the only qualitative synthesis to generate evidence about experiences of living with CML and adhering to prescribed medication. Consequently, we are unable to compare our findings with similar work. Major strengths include a robust search strategy, last updated in September 2019; inclusion of 320 patients; two researchers checking study eligibility, codes and themes; and use of NVIVO computer software to facilitate data management and retrieval. The studies we included originated from different countries, some of which described systems of free access to TKI medication, and others that did not clarify this. However, as all the studies had inclusion criteria that the patient was receiving a TKI medication, presumably those patients in the studies all had access to their medication. Also, as findings were relatively consistent across studies, we expect our analysis is largely transferable to other regions, where patients access TKIs. The synthesis may be limited by the exclusion of grey literature and articles not written in the English language, which could not be fully searched due to time-constraints; however, the authors were not aware of any ongoing work that might impact on study findings.

Included studies (Table 3) also had limitations. Overall, several lacked a thorough reporting of methods, particularly sampling strategies (e.g. inclusion criteria and reporting on excluded participants), and in the application of theoretical models to data analysis. For example, Wu et al. (2015) used interpretative phenomenological analysis (IPA), but did not describe how its features were implemented in the analysis,

including the impact of the researchers' own conceptions on the findings. Strengths were mostly in the reporting of results. Although this varied from descriptive to more conceptual accounts, there was consistency between the data and results, quotations were used appropriately, and findings were generally presented clearly.

Regarding clinical implications, unmet need and outcomes can be appropriately measured using the CCEQ. Survivorship programmes, individualised and developed for patients with CML, would provide the opportunity for discussions about side effects and adherence, enabling HCPs to understand the patient's perspective and understanding, and meet educational requirements, as necessary. Such care should be supported by systems that allow adequate time and resources for this, with a defined role for primary care HCPs, including GPs and practice nurses. Crucially, of greatest value to patients is a caring approach among HCPs, supported by the creation and maintenance of a culture of kindness and compassion (Campling, 2015).

Development of survivorship programmes or other interventions to support self-management in CML requires further qualitative research to investigate the experiences of those caring for people with CML. This should also examine contextual issues for patients, such as social support, views on hospital care and disease knowledge. Recent publications have begun to emerge that suggest some patients may now safely discontinue TKI medication (Clark et al., 2017; Etienne et al., 2017; Saussele et al., 2018). Further qualitative research exploring the experiences of such patients, alongside the QOL measures used in these studies, will add depth to our understanding of this new challenge for patients.

8. Conclusion

This synthesis has demonstrated the significant impact CML and TKI treatment have on patient wellbeing and day to day life. As with an increasing number of cancers, CML involves the self-management of treatment at home, outside the clinical environment. Our synthesis provides evidence that, in the home-setting, patients develop their own strategies to manage adherence and side effects, often not discussing this with HCPs. CML self-management occurs within the context of the individual's own knowledge and perceptions of their disease, as well as the influence of their HCP and the nuances of the health system providing care. As in other chronic cancers, little research exists about experiences and survivorship in CML, or the perspectives of HCPs. However, given that treatment is administered at home, the development of survivorship programmes or interventions should perhaps look beyond a medical model of disease management, to a more a community-based social model, delivered with the support of primary care teams, in a setting familiar to patients and where they live their lives. Such an approach, which has the capacity to adapt to individual contexts and choices, may be most appropriate to develop mechanisms for supporting patient decision making and disease management strategies.

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Declaration of competing interest

All the authors declare they have no conflict of interest that could inappropriately influence this study.

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Appendix 5 REC approval letter



Health Research Authority

Yorkshire & The Humber - Leeds West Research Ethics Committee

Room 001, Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0207 104 8087

31 March 2016

Miss Ann Hewison
ECSG, Department of Health Sciences
Seebom Rowntree Building
University of York
York
YO10 5DD

Dear Miss Hewison

Study title:	Investigating socio-medical factors related to the socioeconomic difference in chronic myeloid leukaemia survival in Yorkshire and Humberside
REC reference:	16/YH/0016
Protocol number:	N/A
IRAS project ID:	173262

Thank you for your letter of 21 March 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Christie Ord via nrescommittee.yorkandhumber-leedswest@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a **favourable** ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ('Participant Identification Centre'), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management
A Research Ethics Committee established by the Health Research Authority

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see 'Conditions of the favourable opinion' above).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Confirmation of any other Regulatory Approvals (e.g. NIGB) and all correspondence [YHHN register consent form]		
Covering letter on headed paper		18 December 2015
Covering letter on headed paper		
Covering letter on headed paper [Response to Provisional Opinion]		21 March 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University of York indemnity insurance]		31 July 2015
GP/consultant information sheets or letters	Version 2	18 March 2016
Interview schedules or topic guides for participants	Version 1	27 November 2015
Letter from funder [Signed application form for university funded PhD study]		06 May 2014
Letter from funder [Signed PhD department funding application]		06 May 2014
Letters of invitation to participant [Patient interview invitation letter]	Version 1	27 November 2015
Letters of invitation to participant [Practitioner invitation letter]	Version 1	27 November 2015
Letters of invitation to participant [Patient questionnaire invitation letter]	Version 1	27 November 2015
Other [Leeds West REC approval for YHHN register]		03 September 2004
Other [PhD acceptance letter]		22 July 2014
Other [PIAG approval for YHHN register]		22 August 2007
Other [YHHN consent form]	Version 10	10 August 2015
Other [Summary CV for second supervisor Prof K. Atkin]		27 November 2015
Participant consent form [Patient interview consent form]	Version 2	18 March 2016
Participant consent form [Practitioner consent form]	Version 2	18 March 2016
Participant information sheet (PIS) [Patient interview information sheet]	Version 2	18 March 2016
Participant information sheet (PIS) [Patient questionnaire information sheet]	Version 2	18 March 2016
Participant information sheet (PIS) [Practitioner information sheet]	Version 2	18 March 2016
REC Application Form [REC_Form_15012016]		15 January 2016
Research protocol or project proposal	Version 1	27 November 2015
Summary CV for Chief Investigator (CI)		18 December 2015
Summary CV for supervisor (student research)		18 December 2015
Summary CV for supervisor (student research)		27 November 2015

Statement of compliance

A Research Ethics Committee established by the Health Research Authority

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document '*After ethical review – guidance for researchers*' gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

16/YH/0016

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely
pp



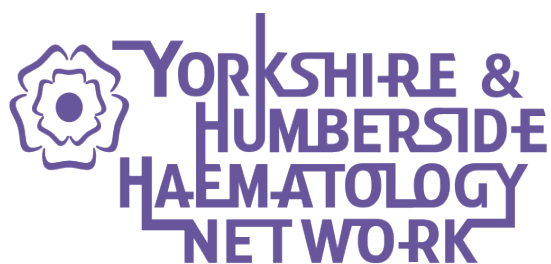
Dr Sheila E. Fisher
Chair

Email: nrescommittee.yorkandhumber-leedswest@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Sue Final, University of York
Deborah Philips, York Teaching Hospital NHS Foundation Trust

Appendix 6 Patient invitation letter



YHHN
Area 3, Seebohm Rowntree Building
Department of Health Sciences
University of York
York, YO10 5DD
Freephone: 0800 328 0655
Email: enquiries@yhhn.org

<Date>

Dear <Patient's Name>

We are writing to ask you if you would be willing to take part in a research study examining what it is like to live with chronic myeloid leukaemia. It will involve a single interview, lasting about one hour, either in your home or another place of your choosing. You can have someone else (such as a relative, friend or carer) present at the interview if you would like.

The study is set within the Yorkshire and Humberside Haematology Network (which includes the doctors and nurses looking after you at the hospital and researchers from the University of York) and is funded by Bloodwise. A leaflet with further information about the study is enclosed for you to read and to help you decide whether or not you would like to take part.

If you are willing to take part, please contact us on our Freephone number above, by email, or tick and return the slip in the Freepost envelope and we will contact you to arrange an interview. If you do not want to take part you do not need to respond to this letter and we will not contact you again.

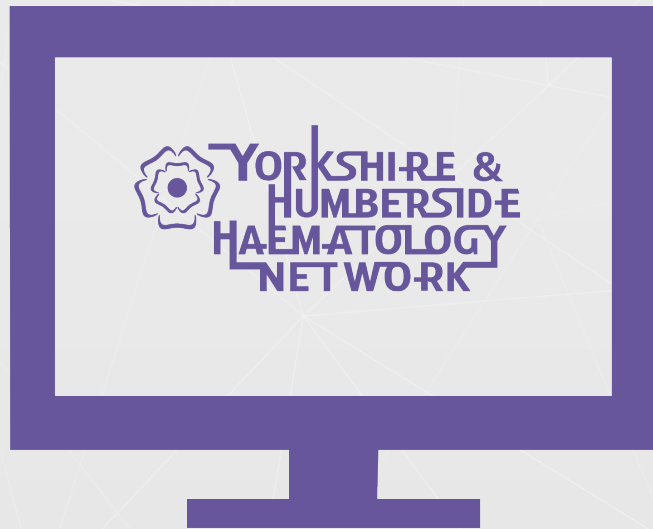
Please do not hesitate to contact us if you need any further information about the study to help you decide whether to take part. Thank you for taking the time to read this letter.

Yours faithfully,

Ann Hewison, Study Nurse

Appendix 7 Patient information leaflet

find us online at:

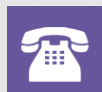


www.yhhn.org

or scan this barcode with your
smartphone QR reader app:



Contact Us



Freephone: 0800 328 0655



Email: ann.hewison@york.ac.uk



Website: www.yhhn.org

Bloodwise

Beating blood cancer since 1960



YORKSHIRE & HUMBERSIDE HAEMATOLOGY NETWORK

Participant Interview Information Leaflet

v2, March 2016



What should I do now?

If you would like to take part, please tick the box on the slip of paper which we sent you and return it to us in the Freepost envelope, ensuring that your details are correct. Alternatively, you could call us using the Freephone number or email – both are shown on the back page of this leaflet. If you feel unable to participate, then no further action is required and we will not contact you again.

What if I change my mind?

You can change your mind and withdraw from the study at any time without giving a reason. If you wish to do this, please contact us using the details on the back page of this leaflet. Any information you have given will be destroyed. Whatever your decision, it will not affect the standard of care you and your family receive.

Standard NHS indemnity arrangements apply to this research.

What is the purpose of this study?

You are being invited to take part in a research study. Please take the time to read this leaflet carefully and to discuss it with other people if you wish. Please contact us if there is anything that is not clear or if you would like more information – our contact details are on the back page of this leaflet.

The purpose of this study is to investigate what it is like to live with chronic myeloid leukaemia. By talking to people with this disease, we hope to find out what factors affect how they cope. We will ask you about your diagnosis, treatment experience, follow up care and general health and quality of life, so that we can understand how this varies among different people. This information will help us to understand where changes could be made that would improve the way that chronic myeloid leukaemia is managed.

Who is doing the study?

The study is being carried out on behalf of the Yorkshire and Humberside Haematology Network (YHHN), which includes the doctors and nurses responsible for your care, and researchers in the Epidemiology and Cancer Statistics Group (ECSG) at the University of York. The research is led by an experienced study nurse from ECSG who is also a student researcher and will be carrying out the project as part of a PhD. YHHN is funded by Bloodwise (registered charity number 216032).

Why was I chosen?

In the Yorkshire and Humberside region around 35 people are diagnosed with chronic myeloid leukaemia each year. We want to interview around 20 of these people in order to understand their different experiences and that is why we have written to you.





Why should I help?

The information collected from you and other participants will lead to a greater understanding about the care of people with chronic myeloid leukaemia. We hope that this will identify changes that can be made in the way that people with this disease are cared for, which will benefit others in the longer term by ensuring that everyone receives the best possible care.

What does the study involve?

The study will involve an interview lasting a maximum of one hour, depending on how you are feeling that day. This will be carried out by an experienced nurse who is also a research student from the ECSG study team. The interview can take place at your home, the University of York or another place where you feel comfortable. If you wish, you are welcome to have a relative or carer present during the interview and they can take part too if you would like. Any travelling expenses will be reimbursed.

With your permission, the interview will be recorded and a typed copy will be made so that we can fully assess what you have said and look at this alongside the views of other patients. After the interview has taken place, you will be given the name of a nurse you can contact if you feel you would like to have a further discussion about any issues that arise during the interview. With your permission, we will also inform your GP and/or hospital team that you have taken part in the study.

In the meantime, if you need more information to help you decide whether to take part, please contact us using the details on the back page of this leaflet.

Will I be given any results?

The results of this study will be available on our website (www.yhhn.org) and in YHHN Newsletters, which are routinely sent to YHHN patients. Findings will also be published in scientific journals and presented at conferences when the study is completed.

Will the information be kept confidential?

Yes, any information you provide is totally confidential. If you agree to take part in the study, we will use a code number to identify you and any information you give to us. This means that no-one will be able to trace or identify you. Your details will not be passed on to anyone else.

The study has approval from a Research Ethics Committee which includes doctors, nurses, other health professionals and lay people. Any information you provide is kept in accordance with the Data Protection Act. Information is processed by dedicated staff working on the study, all of whom have been trained in confidentiality procedures.

Your interview will be used by the researcher during the course of the study. After a further 5 years the recording and any paper copies of the interview will be destroyed. It should be noted that we may have to inform relevant professional authorities in the unlikely event you tell us that you, or anyone else, is at risk of harm. Also, if we consider your health is at risk because of anything you tell us we will encourage you to contact your GP, hospital doctor or nurse and we reserve the right to do this for you, if necessary.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you decide to take part you can withdraw at any time and do not have to give a reason. Your decision will not affect the standard of care you or your family will receive, or your relationship with the doctors and nurses caring for you.

Appendix 8 Practitioner invitation letter



YHHN
Area 3, Seebohm Rowntree Building
Department of Health Sciences
University of York
York, YO10 5DD
Freephone: 0800 328 0655
Email: enquiries@yhhn.org

<Date>

Dear <Practitioner>

We are writing to ask you if you would be willing to take part in a research study to investigate survival differences in patients with chronic myeloid leukaemia. This will involve a single interview, lasting a maximum of forty minutes, at a place of your choosing.

The study is set within the Yorkshire and Humberside Haematology Network (YHHN – www.yhhn.org), which forms the core of the Haematological Malignancy Research Network (HMRN - www.hmrn.org). YHHN is a specialist population based registry which is managed by the Epidemiology and Cancer Statistics Group (ECSG) at the University of York and is funded by Bloodwise. A leaflet with further information about the study is enclosed for you to read and help you decide whether or not to take part.

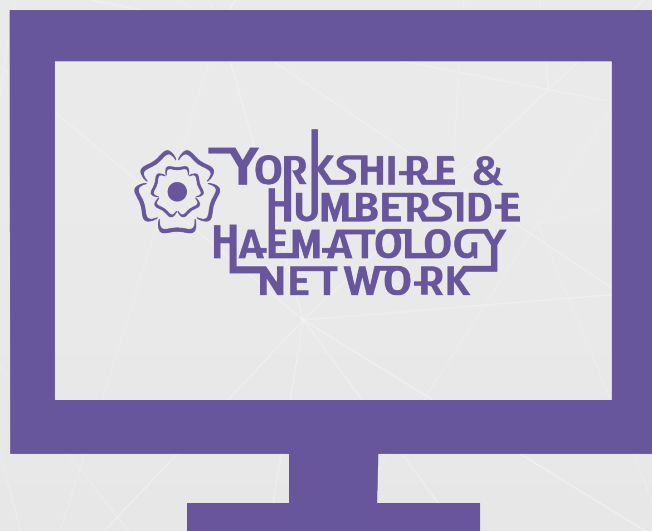
If you are willing to take part, please contact us on our Freephone number above, by email (details on the back of the enclosed leaflet) or tick and return the slip below in the Freepost envelope provided and we will contact you to arrange an interview. Please do not hesitate to contact us if you need any further information about the study. Thank you for taking the time to read this letter.

Yours faithfully,

Ann Hewison, Study Nurse

Appendix 9 Practitioner information leaflet

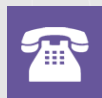
find us online at:



www.yhhn.org



Contact Us



Freephone: 0800 328 0655



Email: ann.hewison@york.ac.uk



Website: www.yhhn.org

Bloodwise

Beating blood cancer since 1960

Practitioner Information Leaflet

What should I do now?

If you would like to take part, please tick the box on the accompanying letter and return it to us in the Freepost envelope ensuring that your details are correct. Alternatively, you could call us using the Freephone number or email – both are shown on the back page of this leaflet. If you feel unable to participate, then no further action is required and we will not contact you again.

What if I change my mind?

You can change your mind and withdraw from the study at any time without giving a reason. If you wish to do this, please contact us using the details on the back page of this leaflet. Any information you have given will be destroyed and you will not be contacted again.

Standard NHS indemnity arrangements apply to this research.

You are being invited to take part in a research study. Please read this leaflet and contact us if there is anything that you would like more information about – our contact details are on the back page of this leaflet.

What is the purpose of this study?

Patients with chronic myeloid leukaemia (CML) who live in more deprived areas of Yorkshire and Humberside have a significantly worse survival than those who live in more affluent areas. The purpose of this study is to investigate what might be causing these differences. We will explore this via interviews with clinical staff caring for people with this disease including consultant haematologists, haematology doctors and clinical nurse specialists. We will ask questions about what guides haematology practice, issues involved in caring for patients such as medication adherence and patient education, as well as how care is organised.

This will complement information collected from CML patients themselves about their diagnosis, treatment experience, follow-up care, general health and wellbeing, and quality of life.

Information from interviews with staff and patients will be used in a questionnaire which will be sent to a wider group of CML patients. Study findings will highlight variables associated with survival differences, which will underpin recommendations for future changes to practice that may improve care and outcomes in CML.

Who is doing the study?

This study is being organised by the Yorkshire and Humberside Haematology Network - YHHN (www.yhhn.org), which is managed by researchers from the Epidemiology & Cancer Statistics Group (ECSG) at the University of York and funded by Bloodwise (registered charity number 216032). It is part of a PhD project being carried out by an experienced ECSG study nurse.

Why was I chosen?

You have been chosen as a potential participant because you are a member of the clinical team providing care for people with CML at one of fourteen hospitals within the YHHN study area.

Why should I help?

The information collected from you and other practitioners will help our understanding about the care pathways of patients with CML. We hope that this will lead to the identification of changes that could be made in the way that patients with this disease are managed. This will benefit others in the longer term by ensuring that everyone receives the best possible care.

What does the study involve?

The study will involve an interview with an experienced ECSG study nurse who is also a PhD student. This will last a maximum of forty minutes and will take place at a location of your choice. With your permission, the interview will be recorded and a transcribed copy will be made so that we can fully assess what you have said and look at this alongside the views of other clinical staff and patients.

In the meantime, if you need any further information please contact us using the details on the back page of this leaflet.

Will I be given any results?

The results of this study will be available on our website (www.yhhn.org) and will be discussed at YHHN clinical meetings. Findings will also be published in peer-reviewed journals and presented at conferences when the study is completed.

Will the information be kept confidential?

Any information you provide is totally confidential and will be kept in accordance with the Data Protection Act. Information is processed by dedicated staff working on the study, all of whom have been trained in confidentiality procedures. The study has approval from a Research Ethics Committee.

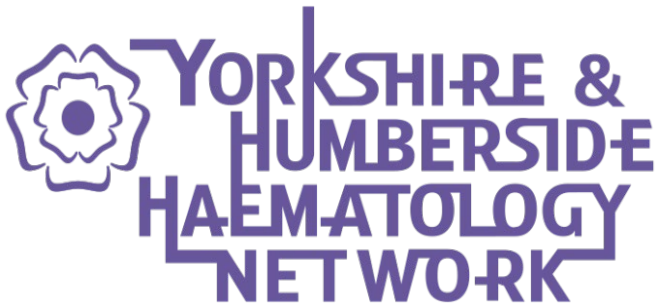
If you agree to take part, we will use a code number to identify you and any information you give us. This means that no-one will be able to trace or identify you. Your details will not be passed on to anyone else.

Your interview will be used by the researcher during the course of the study. After a further 2 years, the recording and any paper copies of the interview will be destroyed.

Do I have to take part?

No, it is up to you to decide whether or not take part. If you decide to take part you can withdraw at any time and you do not have to give a reason.

Appendix 10 Interview schedules



Living with chronic myeloid leukaemia: Patient interview schedule

Pre-interview

- Introduce self
- Explain study
- Explain interview: time, recording, confidentiality
- Explain and complete consent form

Can you describe your diagnosis of CML and your understanding of it over time?

- Experience of diagnosis
- Time from diagnosis to treatment
- Type of medication (in trial?) and changes

- Understanding of CML at the time, and now?
- Understanding of medication at the time, and now?
- Understanding of response at the time, and now?
- Advice from Dr/nurse at the time and since?

How has your treatment been since diagnosis?

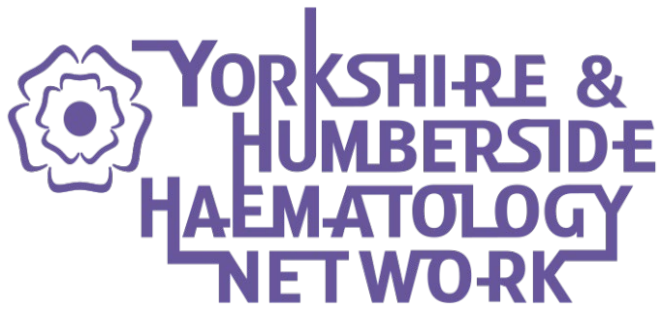
- What helps you to take your medication?
- Are there any times when you haven't taken your medication as prescribed?
- If missed: How many times (when?), all the reasons why, what happens? (any ill effects/response), what action do you take?, do you inform Dr/Nurse?
- Side-effects and how they are managed (do you discuss with Dr/Nurse?)
- Process of obtaining medication

How is your general health/quality of life?

- General health (co-morbs), how does it/they affect day to day life?
- Dealing with general health problems
- Changes to daily life due to CML and any changes to lifestyle since CML?
- Support systems: who is important in terms of support?
- Dealing with concurrent life stresses/events
- How would you expect/hope to see the future in terms of your health?

End of interview

- Is there any advice you would give to other people with CML to help in managing the disease?
- Are there any changes you feel would be helpful to the way you are cared for?



Managing CML: practitioner interview schedule

Practice

What kind of haematology patients do you look after?

- What is your role day to day
- Own practice: job title and how long qualified/worked in haematology
- Any CML patients? How many?
- What is your system of outpatient care for CML patients (i.e. general haem clinic , myeloid, leukaemia, CML specific): who sees the CML patients?
- How do CML patients sit within the context of their other patients? (i.e. what % of workload/clinic time/other inpatients and outpatients) Do you see inpatients?

What guides your practice?

- Own experience, guidelines, colleagues, MDT, drugs reps, research (with CML patients?)
- How do you make treatment decisions about complex cases? E.g. non-responder after 6 months/severe side-effects, high Sokal and low CV risk?
- Many patient had significant co-morbidities: how does this impact on treatment and care (e.g. confusing symptoms, more at risk on treatment)

- What is your process of PCR monitoring CML patients: (and why? Standardised timing as per ELN? Use HMDS online request form?)
- What helps or is unhelpful about the process of monitoring (timing of samples, OPAs, communication with HMDS etc)

Patients

What kind of advice do you give to Haematology/CML patients at diagnosis and over time?

- e.g about treatment, pathway, response?. Any misunderstandings? (e.g. poor prognosis or OK to miss medications) What are common questions patients ask (changes over time)?
- Many pts had a positive outlook, more/less likely to ask for help, understand explanation, adhere? How do you think their own perspective influences how they manage their disease?
- Many pts talk about mental wellbeing, employment, hols/travel. How do haematology cancers/CML impact on quality of life
- What type of patients do well e.g. those with more awareness? (coping strategies/other influences on response?)

What do you think influences adherence to oral medication for haematology cancers/CML?

- E.g. Gender, age, SES, education, co-morbidities, length of time since diagnosis, side-effects...
- How do you identify non-adherence and why do some patients struggle to adhere?
- How do you manage non-adherence: advice, information, support, devices (dosett box, text reminders).

Have you any ideas as to why there is a SE gap in survival in CML patients?

- ?adherence, interaction btw lifestyle choices and CML treatment, differences in treating hospitals... (not seen in incidence. Seen in some other blood cancers: Myeloma+ CLL)

System

Do you see any problems with the organisation of outpatient care for Haematology cancer/CML patients?

- E.g. pressure from more acute patient care, prescriptions which run out, clinic waiting times, delayed results....(patients: lack of communication both ways, prescription problems, medical procedures)

Do you think there are any changes which may benefit CML patients and their management?

- Better equipped pharmacy, less waiting around at OPAs, more opportunity for patients to talk about their concerns? (patients: nice staff, good explanations, efficiency)

Appendix 11 Consent forms: patient and practitioner



Study Number

Participant Interview Consent Form

Thank you for reading the information about our research study. If you think you would like to participate, please read and sign this form. Please initial the boxes below if you agree with the statement.

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| 1. I have read the attached information leaflet (Version 2, March 2016) and have been given a copy to keep. I have been able to ask questions about the project and I understand why the research is being done. | <input type="checkbox"/> |
| 2. I understand that my participation is entirely voluntary and I will not receive any payment. I am free to withdraw my consent at any time without giving a reason. | <input type="checkbox"/> |
| 3. I am willing to take part in an interview with a researcher. | <input type="checkbox"/> |
| 4. I am happy for this interview to be recorded and transcribed. | <input type="checkbox"/> |
| 5. I am happy for my GP and the clinical team at the hospital to be informed that I have taken part in this research. | <input type="checkbox"/> |
| 6. I understand that all the information I give will be treated confidentially and will not be released in such a way that I could be identified. I am aware that the data will be used anonymously. | <input type="checkbox"/> |

Name (CAPITALS)

Signature

Date

Participant Interview Consent Form: v2, March 2016



Study Number

Practitioner Consent Form

Thank you for reading the information about our research study. If you would like to participate, please read and sign this form. Initial each box below if you agree with the statement and sign at the bottom of the page.

1. I have read the attached information leaflet (Version 2, January 2018) and have been given a copy to keep. I have been able to discuss the study and understand why it is being done.

2. I understand that my participation is entirely voluntary and I will not receive any payment. I am free to withdraw my consent at any time without giving a reason.

3. I am willing to take part in an interview with a researcher.

4. I agree that this interview can be recorded and transcribed.

5. I understand that all the information I give will be treated confidentially and will not be released in such a way that I could be identified. I am aware that the data will be used anonymously.

Name (CAPITALS)

Signature

Date

Practitioner Consent Form: v2, Jan 2018

Appendix 12 Annotated patient transcript (excerpt)

30 PA04 Well everything they did helped me. Do you mean
31 psychologically helpful or do you mean...?

32 AH Either I suppose. Help with either a practical help with just
33 your medication and

34 PA04 I didn't need that. I mean it was simple enough. It was just
35 taking one tablet a day, you know, I didn't need any help with
36 that.

No help
needed
with
medication

37 AH So perhaps a bit of emotional support or advice you got?

38 PA04 Well again I have my family. I've got daughters and they gave
39 me a lot of support. I am a nurse myself. I did my full training
40 and I'm midwife as well and a health visitor, so you know, I
41 knew a great deal anyway to comfort myself. I really thought
42 my end had come, I mean, I was very relieved to know that
43 there was a treatment. I remember asking the doctor whose,
44 what was his name? Dr [name] – I've forgotten his name.

Didn't need
emotional
support
family
support.

45 AH At ?

Diagnosis: Partial thoughts of
poor prognosis

Relief at
treatment
available

46 PA04 Yes. He worked with (consultant name) but I remember
47 asking him, how long do I have, you know, I need to know?
48 And he said, well I don't know. Five years. We expect 5
49 years because he said we can only say 5 years because
50 that's as old as the drug is that you're having, so we don't
51 know any more than that but we know people that have been
52 on it for 5 years and they're fine. So that was a great relief
53 and of course I'm still here which is amazing.

Relief at
prognosis
explanation
from
consultant.

54 AH Even more a hopeful picture now isn't it. So 2008 was it?

55 PA04 Yes, yes...

Good
interpretation
understanding of
prognosis

56 AH So for a short time it sounds like, you know, you thought all
57 sorts, you didn't know until they gave you that tablet really that
58 you could be treated quite well?

Treatment
at

59 PA04 Yeah, but it was a short time, it was amazingly short, I was
60 gobsmacked really by the way they treated me, you know, it
61 was wonderful.

diagnosis
wonderful.

62 AH And in terms of the treatment, do you think you've learnt more
63 about that over the years or do you think you've learnt what
64 you needed to know and not much has changed really....?

Appendix 13 Final patient transcript coding frame

CML perspective over time

Pre diagnosis delay

Pre diagnosis: symptoms

Pre diagnosis: no symptoms

Initial shock at diagnosis

Poor prognosis

Making sense of diagnosis

Current perspective: positive outlook

Current perspective: uncertainty

Current perspective: negative outlook

Hopes for a normal symptom free life and death

The future: uncertainty

The future: negative outlook

The future: positive outlook

Advice and understanding

Lack of disease knowledge:

- Disease treatment
- Disease pathway
- Disease response
- Managing medication

Good disease knowledge:

- Disease response

- Disease pathway
- Disease treatment
- Treatment patterns
- Treatment/disease complications
- Side-effects
- Managing medication
- Co-morbidities

Doesn't seek, want/need advice

Wants or seeks advice, support and information:

- Disease treatment
- Disease pathway
- Questions or interested about disease
- Information format
- Support from others
- Too much information
- Disease response

Treatment

Prompt treatment start/diagnosis

Delayed treatment start or diagnosis

TKI failure

Successful treatment

Side-effects to TKIs/CML:

- GI
- Pain
- Not clear if related to CML/TKI
- Fatigue
- Respiratory
- Blood counts
- Skin and hair
- Oedema
- Cardiovascular
- Neurological

- Allergy
- Slight
- Infection
- Mood changes
- Tinnitus

No side-effects to TKIs

Managing side-effects independently

Manages side-effects with professional advice

Side-effects impact on missed medication

Switch or dose change or stop due to side-effects

Managing medication

Missing medications occasionally

Not missed medication

Unintentional missing medication:

- Forgetting
- Change to routine
- Prescription problems
- Illness
- Polypharmacy
- Tiredness

Intentional missing medication:

- Instructed by Dr
- Patient choice

Strategies to support adherence:

- Routine
- Polypharmacy
- Device or alarm
- Family members
- Good memory
- Buffer supply
- News on radio

Missing medication causes no side-effects

Missing medication causes side-effects

Missing medication doesn't effect response

Uncertain if missing medication effects response

Concerned about the effect of missing medication on response

Discussed missing medications with Dr/Nurse

Not discussed missing medications with Dr/Nurse

Co-morbidity

Manages co-morbidities independently

Help from professionals to manage co-morbidities

Interaction of CML and comorbidities

Co-morbidities confuse symptoms

Co-morbidities impact on daily life

Co-morbidity has no impact

Co-morbidities have a greater impact than CML

Health care services/professionals

Changes to care for the better:

- Nurse telephone clinic
- Prescriptions
- Hospital buildings

Unhelpful changes to care:

- Prescriptions
- Nurse Telephone clinic

Changes to care reasons:

- Unclear
- Backlogs

- Less waiting time in hospital
- Financial

Changes patient made to improve care

Hospital follow up: a predictable routine

Rarely uses hospital CML team

Rarely uses GP/Primary care

Preferred health care professional for general health

Positives about hospital care:

- Nature of staff
- Good explanations
- Efficiency
- Psychosocial support
- Disease tests and treatment
- Relationship with staff
- Prescriptions
- Specialist care
- Sees same doctor
- Organisation of appointments

Negatives about hospital care:

- Lack of communication
- Prescriptions
- Medical procedures
- Waiting
- Transport
- Missed or delayed tests, results or letters
- Disease treatment and care
- Feels a nuisance or fraud
- Different Doctors
- Communication with Doctors
- Unable to use computer

Positives about primary care:

- Efficiency
- Good relationship with GP

- GP listens
- Special treatment
- Reliable
- Accessibility
- Private room

Negatives about primary care:

- Poor care
- Little CML knowledge
- Availability
- Lack of explanation

Social services inadequate

Quality of Life

CML impacts daily life:

- Mental wellbeing
- Employment
- Holidays or travel
- Sport
- Meals and alcohol
- Caring for household
- Getting around
- Positive lifestyle changes
- Socialising
- Appearance
- Whole life change

CML has no impact on daily life

Death or loss of loved ones

Loss of career/hobbies/ADLs

Need for independence

Other people's reaction

Supportive family and other people:

- Sharing emotions
- Family are supportive
- Advocacy
- Help with practical tasks
- Supportive employer or employees

- Friends are supportive
- Help with transport
- Voluntary/charitable organisations
- Companionship
- Personal Care
- Emergency contacts
- Faith
- Potential donors

Lack of support from family and other people

Supports family

Stresses within family/ others

Incongruous laughing

Pastimes

Social issues; impact on daily life

Appendix 14: Final practitioner transcript coding frame

Clinical Practice/set up

CML patients take up more time than others

CML patient number or workload small in comparison to others

CML patients stable or uncomplicated

CML patients not always stable or simple

What guides medical practice

- Cardiovascular risk
- Co-morbidity
- Guidelines
- Research
- SOP
- Communicating with colleagues
- Regional CML consultant lead
- Senior clinical scientist HMDS
- Clinical trials
- Clinical supervision
- Investigations
- Pharmacy
- MDT
- Linking up nationally
- Conferences
- Network meetings
- Senior clinician
- Familiarity with drugs
- Risk score
- National experts
- Drug profile
- Meetings
- Journal club
- Speakers
- Patient age
- CML registry
- Patient need
- What TKIs are available
- The pharmaceutical industry

Switching meds depends on precise monitoring

Switching meds depends on cardiovascular risk

Switching meds: need to check adherence

Switching meds: MDT

Switching meds due to SEs

Molecular monitoring is precise

Monitoring done routinely

Monitoring results delayed

Trial monitoring less than national guidance

Stopping TKIs

Difference in practice between hospitals

- Sees OPs mostly/ only
- Sees OPs and IPs
- CML interest/specialist
- Generalist
- OP CML specific clinics
- General OP clinics
- Remote monitoring
- Differences in OOA hospitals
- Differences in pharmacy service
- Within the region
- Differences in patient populations
- TYA patients with CML interest

GP/Primary care involvement

- Dealing with co-morbidity
- GPs could manage prescriptions

- Help to contact patient
- Inappropriate management of TKIs
- Prolonged wait for blood test for remote monitoring
- No specialist knowledge
- Little input

Significant experience in haematology

Limited experience

CNS role

- CML specialist clinic
- Others

Clinician anxiety over patients

- Significant illness due to treatment
- Deterioration due to NA
- Dealing with different personalities

Clinic negatives

- Waiting with acutely ill patients
- Over-running clinic
- Waiting time in clinic
- Remote monitoring: lose touch with adherence
- Waiting time for psychology
- Remote monitoring – lack of written info on side-effects
- Remote monitoring – need to take responsibility
- Remote monitoring – transport of bloods
- Incomplete prescriptions
- Pharmacy waiting time
- Regular hospital appointments: patients don't want it
- Delayed monitoring results
- Limited time for discussion in appointment
- Not enough CNS resource
- Hard to monitor prescriptions now electronic
- No clinical trials
- Lack of guidelines
- Change of treatment

Clinic improvements

- Patient information
- Patients prep'ed prior to appointment
- See same doctor
- Consultant knows patients well
- CML dedicated clinic
- Electronic HMDS request form
- Psychological support
- More comments on monitoring reports
- Home delivery of meds
- Up to date results

Clinic positives

- Home delivery of medication
- Remote monitoring – information
- Remote monitoring – convenient
- Remote monitoring - robust
- Dr know patients well
- Pharmacy
- Planning prescriptions
- Flexible appointments
- Accurate records
- Continuity of care
- Specialist diagnostic laboratory
- Bloods done in advance
- Phone clinic
- No improvements needed
- Sees patients even though on phone clinic
- Living with and Beyond Cancer team
- New diagnoses
- Monitoring
- Lines of treatment available

Suggested improvements

- Phone clinic
- Remote monitoring
- Home delivery of meds
- More time with patients
- Linking up patients
- More community health care involvement
- More nurse led care
- Patient access to results
- TKIs with no side-effects
- Guidelines for nurse led clinic

- Increased CNS resource
- Short waiting time
- Clinics prep'd in advance
- More support for patients

Hospital care negatives

- Other specialities unaware of TKI treatment

Quality of life/side-effects

CML doesn't/ has little impact on daily life

QOL unclear link with molecular response

CML impact:

- Travel and travel insurance
- Use in order to claim benefits
- Shock at diagnosis
- Harder for younger people
- Easier for older people
- Individual
- Fatigue
- Employment
- Don't discuss with doctor
- Harder for those with side-effects and not used to the UK
- Anxiety
- Eating
- Socialising
- Awareness of ongoing treatment
- Having to remember
- Getting life insurance
- Buying a house
- Life changing
- Education

Patient perspective

- Most are positive in outlook
- Positive outlook effects adherence
- Negative outlook
- Awareness of risks
- Positive outlook helps with coping/QOL
- Relationship to survival unclear
- Positive outlook effects outcome

- Accepting

Socioeconomic gap in survival reasons or why do some people do better than others

- Education
- Lifestyle
- Family
- Environmental factors
- Language problems
- Family situation
- Relationship with adherence not clear
- Adherence
- Multifactorial
- Lack of continuous treatment
- Learning disability
- Social situation
- Unclear
- Mental Health problems
- Drugs and alcohol

TKIs are well tolerated/ side-effects rare

TKIs are not always tolerated

Side-effects do occur

- Pleural effusion: one e.g.
- Pulmonary hypertension: one e.g.
- Fatigue
- GI
- Low level
- Periorbital oedema
- Multiple
- Nausea
- Cardiac
- Skin rash
- Mental health problems
- Muscle cramp and weakness
- Liver failure

Side-effects or symptoms complicated by co-morbidity

Co-morbidity does not complicate treatment

Side-effects complicated by social/psychological issues

Treatment complicated by co-morbidity

Patients motivation to report side-effects

- Don't want to bother doctor
- See it as low level or manageable side effect
- Waited too long in clinic
- Reports to CNS
- Reports to GP
- Unable to self-manage
- Related to gender

Poor management of side-effects

- Fatigue
- GI

Active management of side-effects

- Medical management
- Communication
- Age and co-morbidity
- Awareness of SEs
- Information and awareness
- GP's job
- Switching TKI
- Keeping fit

Patient management of side-effects

- Diarrhoea

Side-effects – patients have to live with them

Advice

Advice at diagnosis

- Adherence
- Switching drugs
- Written info
- Verbal explanation
- Extra appointment

- Ongoing advice
- Stopping TKIs, change in advice
- CNS role
- How we can help
- Explanation of the service
- Side-effects
- Communication
- Reassurance
- Healthy lifestyle
- Lead a normal life
- SCT
- More at diagnosis than later on
- Other services
- Treatment
- Holidays
- Employment
- Dietary
- Disease information
- Pregnancy
- Manage expectations
- Getting insurance
- Buying a house
- Prognosis

Advice on prognosis:

- Balanced: not always a 'good' leukaemia
- Avoided in older diagnoses?
- Good prognosis
- Risk of acute leukaemia
- Stopping TKIs

Ongoing advice

Adherence

Intentional non-adherence

- Rejection of service/advice
- Trying for a baby
- Side-effects
- Alcohol/drugs
- Younger age
- Denial
- HCP advice

- Complacency over time
- Social circumstances
- Mental health issues
- Individual psychology
- Co-morbidity
- Effect on appearance
- Illness

Unintentional non-adherence

- Forgetting
- Don't think it's important
- Miscounting meds
- Lack of awareness
- Social circumstances
- Mental Health

Unclear type of non-adherence

Good adherence

Identifying non-adherence

- PCR
- Prescription should have run out
- Asking patient
- DNAs appointments
- Blood counts
- Remote monitoring
- Enlarged spleen
- BMAT
- Patient tells HCP
- PCR not reliable
- Difficult to monitor
- Mutational analysis
- Being suspicious
- No periorbital oedema

Informing HCP about non-adherence

- Patient initiated
- HCP initiated

Not informing HCP about non-adherence

Most people adhere

Adherence motivation

- Fear
- Trust in service

Managing adherence

- Advice at diagnosis
 - Advice on routines, prompts and contraindications
 - Advice on breaks in treatment
 - Advice on outcome
 - Motivational interviewing course
 - Psychology referral
 - Dialogue with patient
 - Monitoring PCR and blood counts
 - CNS role
 - Referral to colleague
 - Unclear parameters
 - Chasing up patients
 - Telling patient to take medication
 - Involving family
 - Advice about switching
 - Switching medication
 - Managing side-effects
 - Managing co-morbidity
 - Adapting dose
-
- Patient support group
 - 'drifted off'

Abbreviations

BAASIS	Basel Assessment of Adherence to Immunosuppressive Medications Scale
BCR-ABL	Fusion gene found on the faulty Philadelphia chromosome monitored in the blood samples of many CML patients
BMQ	Brief Medication Questionnaire
CASP	Critical Appraisal Skills Programme
CCEQ	Chronic Cancer Experiences Questionnaire
CCyR	Complete Cytogenetic Response
CHR	Complete Haematological Response
CLL	Chronic Lymphocytic Leukaemia
CML	Chronic Myeloid Leukaemia
CNS	Clinical Nurse Specialist
CTCAE	National Cancer Institute Common Criteria for Adverse Events
DOH	Department of Health
EFS	Event Free Survival
ELN	European Leukaemia Network
EORTCQLQ-CML24	European Organisation for Research and Treatment of Cancer HRQOL CML module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
GI	Gastro-intestinal
GP	General Practitioner
HCP	Health Care Professional
HMDS	Haematological Malignancy Diagnostic Service
HMRN	Haematological Malignancy Research Network
hOCT1	Human Organic Cation Transporter
HRQOL	Health Related Quality of Life
ICD-03	International Classification of Diseases for Oncology third edition

IPA	Interpretive Phenomenological Analysis
MDASI-CML	MD Anderson Symptom Inventory CML module
MDT	Multi-Disciplinary Team
MEMS	Medication Events Monitoring System
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Mixed Methods
MMAS	Morisky Medication Adherence Scale
MMAT	Mixed Methods Appraisal Tool
MMR	Major Molecular Response
MPR	Medication possession ratio
NCCSDO	National Co-ordinating Centre for NHS Service Delivery and Organisation
NCIN	National Cancer Intelligence Network
NCSI	National Cancer Survivorship Initiative
NCRAS	National Cancer Registration and Analysis Service
NICE	National Institute for Health and Care Excellence
PDC	Proportion of Days Covered
PFS	Progression Free Survival
PICO	Population Intervention Control and Outcomes criteria
PROMs	Patient Reported Outcome Measures
QD	Quantitative descriptive
QNR	Quantitative non-randomised
QOL	Quality of Life
QRC	Quantitative randomised controlled trial
QRT-PCR	Real Time Quantitative Reverse Transcription polymerase chain reaction
REC	Research Ethics Committee
SEER	Surveillance, epidemiology and end results programme
SMAQ	Simplified Medication Adherence Questionnaire

SUNS	Survivor Unmet Needs Survey
TFR	Treatment Free Remission
TKI	Tyrosine Kinase Inhibitor
VAS	Visual Analogue Scale
WHO	World Health Organisation
YHHN	Yorkshire and Humberside Haematology Network

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