To my grandfather
Oskar Walter Leander

For never tiring of
answering my questions

"It's a wonderful poison"

Towards a system approach of understanding behaviour, theory and measurements relating to patient adherence to oral anticancer drugs

Thesis submitted in accordance with the requirements of the University of London for the degree of Doctor of Philosophy by

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This thesis describes research conducted at the School of Pharmacy, University of London between October 2006 and September 2010 under the supervision of Dr. Sarah Clifford and Prof. Nick Barber. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

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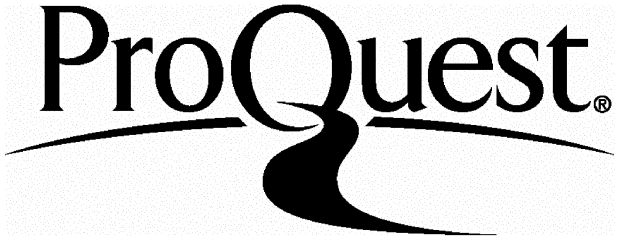

ABSTRACT

Oral anticancer drugs are increasingly prescribed and are often preferred to intravenous treatments by patients. With the introduction of new efficient drugs, cancer is becoming more like a chronic disease that can be managed at home. However, nonadherence to oral anticancer treatments exists and increased prescription of oral therapy prompts further opportunities for nonadherence.

The aims of this thesis were to understand the medication-taking behaviours of chronic myeloid leukaemia (CML) patients prescribed imatinib; to explore the usefulness of the Accident Causation Framework (ACF) in explaining nonadherence; and to develop a self-report diagnostic adherence scale (DAS).

Interviews were conducted with 21 patients whose adherence rates had previously been monitored using MEMS. Analysis was first conducted according to the constant comparison aspect of grounded theory. Subsequently, a framework analysis guided by the ACF was performed. Three pilot studies tested the validity and reliability of the DAS.

Patients commonly missed doses to reduce side-effects or because of forgetting. Surprisingly, many patients did not think missing "the odd dose" mattered and expressed their assurance of this based on communication with health care professionals (HCPs). The ACF could explain reasons for nonadherence and strategies for facilitating adherence. The pilots of the DAS were promising.

Causes of nonadherence should be addressed to improve care and clinical outcomes of CML patients. Patients should be made aware of the dangers of treatment interruptions and of missing relatively few doses. HCPs should avoid using unclear language such as "the odd dose" when discussing adherence issues. Different patterns of nonadherence were revealed, which exposed limitations of using MEMS without self-report measures to support interpretation. A system perspective, based on the ACF, contributed further understanding of medication-taking behaviours; highlighted causes of nonadherence external to the patient and

the need for appropriate adherence monitoring; and may direct strategies to reduce nonadherence.

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LIST OF ABBREVIATIONS

ACF	Accident Causation Framework
BCR-ABL1	BCR-ABL1; a fusion gene of a chromosomal abnormality called the "Philadelphia Chromosome", which is found in 95% of patients with CML. Protein transcripts from this fusion gene are what causes the leukaemia by inducing proliferation of blood cells.
BOPA	British Oncology Pharmacy Association
CCyR	Complete Cytogenetic Response (or Remission); an important therapeutic target for CML patients, where the Ph^+ chromosome is no longer detectable and BCR-ABL1 transcript levels has been reduced by 99%.
CML	Chronic Myeloid Leukaemia
CMR	Complete Molecular Response; a therapeutic target where BCR-ABL1 transcripts are no longer detectable.
DAS/s	Diagnostic Adherence Scale/s
DoH	Department of Health
HCP/s	Health Care Provider/s
MEMS	Medication Events Monitoring System
MMR	Major Molecular Response; a therapeutic target where BCR-ABL1 transcript levels have been reduced by 99.9%.
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPSA	National Patient Safety Agency
PCR	real-time quantitative Polymerase Chain Reaction; a clinical test used to assess the quantity of residual leukaemia in the body by monitoring BCR-ABL1 transcript levels.
Ph^+	Philadelphia Chromosome; a chromosomal abnormality carrying the BCR-ABL1 fusion gene.
RPSGB	Royal Pharmaceutical Society of Great Britain

SCTs	Social Cognition Theories
WHO	World Health Organisation

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Chapter 1: Introduction

1.1 INTRODUCTION

Health behavioural research on treatment adherence has mainly focused on predicting and explaining individual patients' behaviour, and finding ways to modify this behaviour. However, despite over 40 years of research, even the best behavioural theories can only account for a modest amount of the variance in patients' behaviour and adherence enhancing interventions are often found to be of limited effectiveness (Haynes et al., 2008). This may partly be explained by the fact that the theories have only accounted for intentional behaviour, when a large proportion of patients' behaviour has been unintentional. In addition, the focus has been on individual patients whilst the wider health care system's influence on patients' behaviour has largely been ignored. The related measurements developed in the field reflect the narrow individualistic focus and the assumption of behavioural control. It may therefore be time to explore new theories of understanding patients' treatment related behaviours, in particularly theories that take a system wide perspective and can account for both intentional and unintentional behaviours.

Policy drivers worldwide and in the UK are increasingly recognising patients' adherence to prescribed treatment as a priority for improving the population's health (WHO, 2003, Horne et al., 2005, Nunes et al., 2009, DoH, 2010). This increased attention to treatment adherence by policy developers is likely to reflect the facts that people are living longer; that the incidence of chronic illness is increasing and that there is increased focus on providing preventative treatments. Recently the National Institute for Health and Clinical Excellence (NICE) reviewed the evidence on treatment adherence and published guidelines for UK health care services (Nunes et al., 2009). From a policy perspective adherence is also a question of the general safe use of medicines and preventing patients from getting harmed (Nunes et al., DoH, 2010).

Cancer policy for England is set out in the Cancer Reform Strategy (DoH, 2007). The strategy's aims include improving cancer prevention, to speed up the diagnosis and treatment of cancer and to ensure patients can access effective new treatments quickly. However, a recent report showed that the UK lags behind other European countries in providing access to innovative cancer treatments (Richards, 2010). In response to this the UK Health Secretary announced in July 2010 that a fund would be provided to allow clinicians to prescribe drugs that have not yet been approved by NICE (only drugs approved by NICE are funded through the NHS) (DoH, 2010). However, these policy statements on cancer treatment need to be linked to policies that promote treatment adherence to assure patients' safe and effective use of drugs.

In light of the limitations of existing health behaviour theories to explain medication taking behaviour, the general policy context in the UK calls for exploration of new theory that can be used to drive innovative research into reducing the incidence of nonadherence. It can be useful to look at theory from other disciplines for overlaps that can inform theory development and measurements within the field of understanding health behaviours. It has previously been suggested that there are similarities between research into the way patients do not follow their prescribed treatment regimens and research into human errors (Barber, 2002, Barber et al., 2005, Garfield et al., 2009). A possible advantage with using theories explaining human errors, such as the Accident Causation Framework (ACF; Reason, 1990; Reason, 1993; Reason, 2000; Reason, 2001; Reason, 2008), is its ability to explain unintentional behaviour. In addition, the focus is diverted from exclusively examining individual patients' behaviour towards examining the whole system that may influence the patients' ability to take their prescribed treatment, including health care providers (HCPs) and health care policies.

Reason's ACF (1990) was initially developed to explain human errors occurring within industrial settings, such as accidents in the aviation industry or at nuclear power plants. The ACF explains how environmental conditions in which errors are triggered are created by latent conditions such as management decisions and organisational processes. According to this framework, the cognitive functions that

underlie human performance can explain the different ways in which actions fail to reach the desired outcome, either intentionally or unintentionally (Reason, 2008, Reason, 2000, Reason, 1990, Reason, 2001, Reason, 1993). Intentional actions include violations, where the actor knows the right process but chooses not to follow it, and mistakes where the actor does not know the correct process and instead uses mistaken rules or knowledge that leads to failure in reaching the desired outcome. Unintentional slips and lapses are caused by failures of attention and memory. The ACF and how it can be applied to understanding medication adherence will be discussed in more detail in Chapter 3.

There are already examples of recent guidelines and reports approaching patients' ability to follow treatment recommendations from an error and system safety perspective in the case of adherence to oral anticancer medicines (BOPA, NPSA). The patients are no longer seen as solely responsible for taking their medication as prescribed, as their ability to do so depend on the systems being in place to support this "self-administration". In addition, the whole multidisciplinary oncology / haematology team should be involved in the process (BOPA).

This change in perception of medication taking behaviour in relation to oral anticancer drugs seems to have evolved in parallel with the increased focus on developing oral formulations. In recent years many new oral anticancer drugs have been introduced on the market, such as imatinib, nilotinib, dasatinib etc. (NPSA). However, these new oral anticancer drugs tend to be highly toxic with narrow therapeutic indexes similar to the traditional intravenous treatments that are administered by HCPs in a controlled hospital setting. Therefore, the safety issues and the related terminology used to address administration and medication errors of intravenous anticancer treatments, have diffused into the domain of oral anticancer medicines.

Compared to other illness groups, cancer has received limited attention in relation to the way cancer patients' use their medication, in particular concerning malignancies other than breast cancers. It has been widely assumed that cancer patients are unlikely to not take their medication as prescribed because of the seriousness of their illness. However, reviews on cancer patients' medication

taking behaviours, as well as patients with other serious illnesses such as HIV/AIDS, have shown that this is not the case (DiMatteo, Ruddy et al., Partridge et al.). Due to the limited literature on adherence to oral anticancer treatments there have been several calls for further research, with specific calls for research into "real-life" adherence to oral therapies to identify risk factors for nonadherence (Partridge et al., 2002) and to develop better theory for intervention development and measurement (Ruddy et al.).

This thesis will investigate treatment related behaviours of patients with chronic myeloid leukaemia (CML) who are prescribed the oral anticancer drug imatinib, as well as related theories that are used to explain treatment behaviour and the measurements used. When the research of this thesis was initiated in the autumn of 2006 no previous research on adherence to imatinib had been published. Since then one study from the United States that investigated imatinib nonadherence and related health care costs was published in 2007 (Darkow et al., 2007) and one study investigating associations between imatinib adherence and clinical response in CML patients from Belgium was published in 2009, both will be presented in detail in section 1.9.1. The only UK study that has been published on adherence to imatinib and clinical response is the clinical trial we conducted in conjunction with the research presented in this thesis that was published in 2010 (Marin et al., 2010). The interviews presented in this thesis are the first study that has explored the patients' reasons for taking or not taking their imatinib as prescribed. Unless we understand patient reasons for not taking their medicines we cannot intervene to support optimal treatment administration.

Ruddy et al (2009) also specifically called for research into patients' use of imatinib, further highlighting the limited knowledge existing in this area. Therefore, this thesis will mainly focus on behaviour, theory and measurements related to CML patients' use of imatinib. However, there will be many parallels between specific theory and measurements as applied to CML patients on imatinib and general theories and measurements that may be applicable to other patient groups. Thus the thesis will also provide novel contributions to knowledge and critical thinking in the wider field of medication adherence.

This introductory chapter gives an overview of the adherence literature. It begins with discussions of definitions used to describe treatment related behaviours and how these behaviours have been classified. Prevalence and impact of nonadherence across different chronic illnesses will be discussed and factors affecting adherence will be explained. Thereafter, the theories and concepts that have been used to explain behaviour will be critically evaluated and the idea of taking a system perspective using theory derived from explaining human errors to also explain patients' failure to manage their treatment as prescribed will be introduced. This idea was first proposed by Barber in 2002 and will be fully explored in chapter 3 of this thesis. Thereafter, the adherence measurements currently used in the field will be reviewed. Finally the literature on oral anticancer treatments in general will be presented, as well as CML and imatinib in particular. The chapter is concluded by stating the aims and objectives of this thesis.

1.2 DEFINITIONS OF TREATMENT ADHERENCE

Individuals living with a chronic disease, such as asthma, diabetes, hypertension and cancer, are often prescribed long-term treatment regimens. Depending on disease type and stage, the treatment regimen can include one or more medications, and potentially one or more life-style modifications (e.g. diet and exercise) and/or continuous monitoring of bodily functions (e.g. blood glucose level). To follow prescribed regimens can be demanding for individuals, in particular if it infringes on every day routines and activities. Therefore, many persons living with a chronic illness do not follow treatment recommendations as prescribed.

The three most commonly used terms to describe patients' behaviour of following treatment recommendations are compliance, concordance and adherence (Bane et al., 2006). Compliance refers to the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice (Haynes, 1979). Even though Haynes specified that "compliance" is intended to be non-judgemental, the term has now been

disfavoured because of its apparent paternalistic voice, which could undermine the patients' involvement in treatment decisions.

In order to promote patients' greater choice and influence on prescribed treatment researchers and clinicians have therefore endorsed the term adherence. Adherence may be defined as 'the extent to which the patient's behaviour matches *agreed* recommendations from the prescriber' (Horne et al., 2005, WHO, 2003).

The term concordance emphasises an interactive decision making process when prescribing treatment between patient and health care provider (RPSGB, 1997). The term was introduced already in the 70s "to broaden the concept of patient compliance to one of physician-patient concordance" (Hulka et al., 1976 pp 852) and have since then gained increased attention in the adherence research field (Stevenson et al., 2004). The definition of concordance has been somewhat fluid and has been used to describe a range different behaviours and interactions. In general, concordance should not be used to describe patient medication taking behaviour; although some researchers have been found to use concordance synonymously with compliance/adherence (e.g. Johnell et al., 2006). In addition, concordance can be used to describe patient support in medicine taking (Garfield et al., 2007).

Persistence is a fourth term that has been introduced in recent years to describe the length of time a patient stays on a prescribed treatment regimen, from the time of initiation to discontinuation (either by the patient or because the prescribed treatment period has come to an end) (Cramer et al., 2008, WHO, 2003). According to this definition, a patient who takes half of the prescribed daily dose for the prescribed number of days would thus be 100% persistent, although the patient would be considered 50% adherent for the same period of time.

Because of the limitations with using the terms concordance and persistence, as well as the paternalistic tone of compliance, the term adherence will be used throughout this thesis to refer to the extent that patients' behaviour matches prescribed treatment recommendations. The term 'agreed' is purposely excluded from the definition as it is rarely known whether the initial prescriber assured that

the patient agreed to the prescribed regime, although it is acknowledged this may constitute the ideal.

In line with supporting patient choice and influence over their prescribed treatments current UK health policy is moving towards increasingly involving patients in treatment decision (DoH, 2010, DoH. and Farrell, 2004, Nunes et al., 2009). Patient involvement is suggested to increase patient adherence with the treatment regimen, as well as improve health outcomes through patient behaviour modification (Stevenson et al., DoH, DoH. and Farrell, 2004, Nunes et al., 2009). Nonetheless, there are concerns regarding which decisions patients should be involved in and how to best involve the patient in the decision making process, in particular considering professional accountability and the wider policy context (Wirtz et al., 2006). Therefore, it has been suggested health practitioners should strive towards providing patients with the evidence base of their treatment to promote patients' understanding of their illness and treatment with the aim to achieve 'informed adherence' (Horne and Weinman, 2004).

Adherence and nonadherence in turn has many different operational definitions, which is closely linked to how the concepts are being operationalised and measured. These issues will be discussed in-depth in section 1.8. The following section will discuss ways in which researchers have classified different types of nonadherence based on different underlying causes.

1.3 CLASSIFYING NONANDHERENCE

Nonadherence to medication incorporates a range of different behaviours and is due to different causes across patients. Therefore researchers have proposed classification of nonadherent behaviours according to whether the underlying causes were intentional and unintentional, as well as whether prescriptions were not redeemed in the first place or whether dispensed medication was not used as prescribed.

1.3.1 INTENTIONAL VERSUS UNINTENTIONAL NONADHERENCE

In recent years the importance of differentiating between intentional and unintentional nonadherence has been recognised (WHO, 2003, Horne et al., 2005, Lehane and McCarthy, 2007b, Barber et al., 2005). Research has shown this distinction to be important in a range of chronic illness groups (Clifford et al., 2008), including hypertension (Lowry et al., 2005, Lehane and McCarthy), respiratory conditions (Wroe, 2002), HIV (Wroe and Thomas, 2003) and breast cancer (Atkins and Fallowfield, 2006).

Intentional nonadherence refers to patients making a conscious decision to alter or discontinue their treatment and is mainly influenced by the patients' beliefs and motivations, as well as physical experiences of the treatment, such as side effects. Unintentional nonadherence, on the other hand, occurs when the patient intends to adhere to their treatment, but is hindered to do so by factors beyond their immediate control; for example, forgetting to take a dose, not being able to swallow a tablet or limited access to medication. However, some use forgetting as the single definition of unintentional nonadherence (e.g. Wroe, 2002, Atkins and Fallowfield, 2006).

Unintentional reasons for nonadherence seem to be more common than intentional reasons. However, a proportion of the variability between studies is also likely to reflect the different definitions of intentional and unintentional nonadherence across studies, as well as the different research methods and measurements used. This makes it difficult to compare results across studies and to make a general statement. Nonetheless, Clifford et al. (2008) found that 55% of 67 nonadherent primary care patients, who had been prescribed new chronic medications, reported unintentional nonadherence and 45% reported intentional. In a sample of 131 breast cancer patients Atkins and Fallowfield (2006) found that 55% were nonadherent, and of the nonadherent patients 83% reported unintentional nonadherence and 17% reported intentional nonadherence. Another study found that of 198 nonadherent patients prescribed medication for hypertension, 72% reported unintentional reasons, 9% reported intentional reasons and 19% reported both intentional and unintentional reasons (Lowry et

al., 2005). Lowry suggested that the large discrepancy between unintentional and intentional nonadherence in this sample could have been caused by patients being more willing to report having unintentionally missed doses than intentionally choosing to not take their doses. Wroe and Thomas (2003) found that 50% of the total sample of 177 HIV patients on HAART reported unintentional nonadherence and 29% reported intentional nonadherence. Unfortunately, there was no information available to discern whether intentional and unintentional nonadherence overlapped in this sample.

Evidently, the factors influencing intentional and unintentional nonadherence may differ. However, it is likely that many of the factors are interrelated. For instance, a person may unintentionally forget to take their medication and upon remembering that a dose has been forgotten decide not to take it. On the other hand, a person may initially intend to take the medicine, but at the same time believe that the medicine is not that important and therefore be more likely to forget. Nonetheless, it is important to differentiate between intentional and unintentional nonadherence as their different causes may require different solutions (Clifford et al., 2008, Gordis, 1979). It is therefore imperative to consider both intentional and unintentional reasons for not following treatment recommendations when designing interventions (Horne et al., 2005, WHO, 2003). Theories that have been proposed to explain intentional and unintentional behaviours will be discussed in detail in section 1.7.3 of this chapter.

1.3.2 PRIMARY VERSUS SECONDARY NONADHERENCE

Primary nonadherence refers to the patient not redeeming the prescription in the first place. We conducted a systematic review (databases included: Medline, Embase; International Pharmaceutical Abstracts; Pharmline; Cinahl; Psycinfo; and the Kings Fund) of studies addressing error rates in primary care, of which primary nonadherence was one of the definitions of error (Garfield et al., 2009). Two UK studies were identified which showed that 2.9-5.2% of all prescriptions were not cashed (Beardon et al., 1993, Jones and Britten, 1998). Patients' reasons for not cashing prescriptions included being able to get the drugs cheaper over the counter, not wanting to pay copayment and permission from the prescriber to not

cash the prescription (Jones and Britten, 1998), as well as the patient not thinking the prescription is needed (Beardon et al., 1993). In addition, comparing individual prescribers in the study it was found the non-redemption rate were significantly higher for prescriptions issued by trainee doctors, which may suggest that patients had less confidence in their prescriptions and therefore chose not to redeem these prescriptions (Beardon et al., 1993).

Secondary nonadherence refers to the patient not taking medication, which has been redeemed, as it was prescribed (Vermeire et al., 2001). This includes omitting doses, taking extra doses, taking doses at the inappropriate time and discontinuing the treatment. The distinction between primary and secondary nonadherence is particularly useful for understanding the effectiveness of the healthcare system in delivering care to patients. However, only secondary nonadherence (intentional and unintentional) is the focus of this thesis. Nonetheless, all nonadherence can have severe consequences, which will be further discussed in the section below.

1.4 PREVALENCE AND IMPACT OF NONADHERENCE

The prevalence of nonadherence across illness and patient groups has been estimated to be anything from over consumption of medication, through complete adherence to discontinuation of treatment, but averages at about thirty to fifty percent for treatments in chronic illnesses (DiMatteo et al., 2002, DiMatteo, 2004b, Sackett and Snow, 1979, Haynes et al., 2002).

Even though nonadherence is evident in both acute and chronic conditions, research in chronic conditions is often prioritised because of the long term benefits for both individuals and society (WHO, 2003). This is because the primary consequence of nonadherence is reduced efficiency of the treatment, which may in turn lead to illness progression, risks of complications that may need additional treatment and adverse impact on the patients' quality of life. Nonadherence has, for example, been found to be associated with poor control of hypertension (Lowry et al., 2005); reduced efficiency of HAART treatment (Simoni et al., 2006); poor management of asthma (Horne, 2006); and higher risk of diabetes complications (Ciechanowski et al., 2001). The benefit of improving adherence is thus to reduce

the risks of these consequences from occurring and the associated economical burden to society.

Interestingly, it appears that adherent behaviour in itself improves health outcomes. Clinical trials of new medication using placebo as control have found that patients adhering to their placebo treatment have better outcomes than people who are nonadherent to their placebo (Pizzo et al., 1983, Granger et al., 2005, Irvine et al., 1999). This suggests that simply believing a treatment will work may increase the effectiveness of the treatment. Nonadherence due to over ingestion of medication can also have severe consequences including death, in particular when using highly toxic medication with a narrow therapeutic index such as oral anticancer agents (NPSA, 2008).

Nonadherence can constitute a significant bias in clinical trials evaluating the effect of therapeutic agents and it has been argued that adherence rates should therefore always be monitored, controlled during analysis and reported in publications (Boudes, 1998). If the patient has a low level of adherence in the trial this could lead to the selection of an inappropriately high drug dose and potential underestimation of dose related toxicities. Conversely, if the adherence rate is higher in a clinical trial setting compared to normal care, the treatment may not be as effective when released on the market as the trial results suggested.

On a socioeconomic level the impact of nonadherence is substantial. Nonadherence presents an economical strain on health care systems, because of increased likelihood of hospitalisations, complications, and morbidity (Cantrell et al., 2006, Elliott et al., 2005, Sokol et al., 2005). It has been estimated that the cost of unused and unwanted medication exceeds GBP100 million in England (DoH, 2008), and the cost of nonadherence in the United States (US) has been estimated to be USD100 billion (Lewis, 1997). Adherent patients have been found to be associated with the lowest yearly medical cost in the US (Cantrell et al., 2006). Additional costs to society can be estimated by considering the reduced work productivity of patients, and losses related to income and taxes.

Because of the substantial cost of nonadherence, both in terms of the associated reduced clinical benefit for patients and in terms of increased costs to the health

care system, nonadherence has become a priority for health care researchers and policy makers worldwide (WHO, 2003). Indeed it has been suggested that improving nonadherence will have a greater impact on improving the population's health than the development of new medications (Haynes et al., 2008).

Despite the many adverse consequences of nonadherence, at times nonadherence can be desirable. This argument will be examined in the following section.

1.5 NONADHERENCE CAN BE DESIRABLE

Adherence is only desirable when the prescribed treatment is suitable to the patient's condition and capabilities; in effect there are times when nonadherence is the desired behaviour. For example, adherence to medication may cause adverse effects of the drug, such as side effects, to an unacceptable level (Johnson and Neilands, 2007). In such cases nonadherence is sensible in the short term, but may not be ideal from a long term perspective and alternative treatment would need to be considered.

Prescription of inappropriate treatments is also a common occurrence in clinical settings, nonadherence in these circumstances would be the correct behaviour (Smith, 2004). In addition, as knowledge accumulates, treatments that initially were thought beneficial may turn out to cause unexpected harm to patients, such as the increased risk of breast cancer and other illnesses in women who were prescribed postmenopausal hormone replacement therapy (Nelson et al., 2002). That many women were nonadherent to these treatments (Rozenberg et al., 1995) may thus have been reducing harm to these patients. There are of course many different factors that affect adherence to prescribed treatments. The major factors that have been investigated will be discussed in the next section.

1.6 FACTORS AFFECTING ADHERENCE

Adherence behaviour is complex and is influenced by an abundance of different factors. In the literature over 200 factors thought to influence adherence have been investigated, yet very few factors have been shown to be reliably associated with

nonadherence (Haynes, Meichenbaum and Turk, 1987). The following sections will give a brief overview of the most common factors thought to influence adherence. These factors can broadly be categorised into patient related factors, illness and treatment related factors, health care provider related factors and system related factors. It is noteworthy that research methodology and measurement also has a significant effect on adherence outcome data (DiMatteo, 2004b).

1.6.1 PATIENT RELATED FACTORS

1.6.1.1 DEMOGRAPHICS

Demographics are data related to a range of different factors that characterises a person including age, sex, education and socioeconomic status. Many studies have tried to relate such variables with nonadherence to identify patients who are likely to be nonadherent. Correlates between adherence and demographic factors often exist within individual studies. However, reviews have shown that such findings are rarely consistent across different studies (Haynes, Meichenbaum and Turk, 1987). A meta-analysis by DiMatteo (DiMatteo, 2004b) found the following correlations between demographics and adherence:

- Age and adherence NOT correlated
- NO gender differences in adult patients
- Gender differences in paediatric patients (including adolescents), with females being more adherent
- Education positively correlated with adherence in chronically ill patients
- Education NOT correlated with adherence in acute illnesses
- Socioeconomic status positively correlated with adherence if the measure was income specific
- Socioeconomic status NOT correlated with adherence if a general measure of socioeconomic status was used.

Individuals from poor socioeconomic backgrounds may be more prone to nonadherence, as has been found in Sweden (Johnell et al., 2006), Nepal (Mishra et al., 2005), Canada and USA (Kennedy and Morgan, 2006). Particularly in countries,

such as USA, Sweden and Canada, where patients are expected to pay whole or part of their treatment the cost of medication is found to be associated with nonadherence (Heisler et al., 2004, Johnell et al., 2006, Mishra et al., 2005, Kennedy and Morgan, 2006, Kennedy et al., 2004). Furthermore, cost of medicines show particular association with primary nonadherence, as discussed in section 1.3.2 (Johnell et al., 2006).

1.6.1.2 PSYCHOLOGICAL FACTORS

There are several psychological constructs that have been related to nonadherence to treatment regimen, in particular depression and memory.

Depression has been consistently associated with nonadherence. A meta-analysis evaluating the effect of depression on adherence to medication (prescribed for other chronic illnesses than depression) found that the patients who were depressed were 3 times more likely to be nonadherent than patients who were not depressed (DiMatteo et al., 2000).

Memory has also been associated with adherence. Decline in memory functions in older patients contributes to unintentional nonadherence due to forgetting to take medications as prescribed (Bosworth, 2006). In addition, it has been estimated that patients only remember about 50% of what the health care provider communicates in the consultation (Ley, 1988).

1.6.1.3 PAST BEHAVIOUR AND HABIT

Past adherence behaviour has been suggested to be a good predictor of current and future behaviour, i.e. a patient who has been adhering to prescribed treatment in the past is likely to keep doing so (Ogden, 2004). Past behaviour has been shown to influence health related behaviours such as breast self-examination (Hodgkins and Orbell, 1998), binge-drinking (Norman and Conner, 2006) and healthy eating (Conner et al., 2002).

Another aspect of past behaviour is the formation of habits. It has been suggested that adherence might be improved if the patient incorporates their medicine taking

into their daily routines so that medication taking behaviour becomes a habit, which would reduce the conscious effort to adhere (Reach, 2005). Naturally, the patient's habit could be to not take their medication, and such a habit may be persistent and difficult to change.

1.6.1.4 SOCIAL SUPPORT

Social support has consistently been found to be associated with better adherence to treatment regimens. Social support is the support that a patient receives from family and friends both on an emotional and on a practical level. A review from 1976 showed that 5 out of 6 studies had found a positive association between social support and improved adherence (Haynes, 1976a). More recently a meta-analysis provided evidence that social support has a substantial effect on patient adherence (DiMatteo, 2004a). It was further revealed that functional social support (practical, emotional and family cohesiveness) had stronger correlations with adherence than structural social support (marital status and living arrangements). Thus it was argued that it is not necessarily the presence of other people that is important, but the quality of the relationships; although the results also showed that practical support on average has a larger positive effect on adherence than emotional support. This suggest that it might be practical support in terms of reminding to take medicines and help in administer the treatment at home that is the most useful in maintain higher levels of adherence.

1.6.2 ILLNESS AND TREATMENT RELATED FACTORS

There are several illness specific factors that have been studied in relation to patients' adherence to medication, including diagnosis, severity, duration, symptoms and degree of disability. A review by Haynes (1976a) found that severity of illness and diagnosis were related to adherence; adherence rate decreased in illnesses that were mild or asymptomatic. This is particularly important in illnesses such as hypertension where patients generally cannot feel a difference whether they take their medication or not. Indeed they might even experience side effects of the medication, so that the patient feels worse taking the medication than if not taking the medication. In terms of diagnosis, patients

diagnosed with psychiatric illness were less adherent than patients diagnosed with somatic illnesses (Haynes, 1976a).

In the same Haynes (1976a) review it was highlighted that complexity of the treatment regimen was often negatively associated with adherence rate. In line with these results another study found that the number of medication a patient is taking per day is negatively associated with adherence (Stone, 1979). The nonadherence rate for patients prescribed one medication was 15%, for patient prescribed two or three medications 25% and 35% for patients taking five or more medications. A more recent meta-analysis of the association between dosing regimen and adherence rate (measured by electronic monitoring) found that prescribed number of doses is inversely related to adherence rate (Claxton et al., 2001). The analysis found that adherence was significantly higher for once daily versus 3-times daily ($P = 0.008$), once daily versus 4-times daily ($P < 0.001$), and twice daily versus 4-times daily regimens ($P = 0.001$). However, there were no significant differences in adherence rate between once daily and twice daily regimens or between twice daily and 3 times-daily regimens.

1.6.3 HEALTH CARE PROVIDER FACTORS

Health care provider (HCP) factors are less studied than other factors influencing adherence to medications (Hilker, 2007). HCPs can influence patients' adherence through prescribing complex regimen, failing to adequately explain benefit and side effects of the drug, having a poor therapeutic relationship and failing to communicate appropriate information the patient regarding their condition (Osterberg and Blaschke, 2005).

Communication is thought to be the single most important factor that mediates the health care provider's effect on patient adherence. A considerable amount of research has focused on communication between HCPs and patients (Barry et al., Barry et al., Britten et al., Berry et al., 2002, Ciechanowski et al., 2001, Mishra et al., 2006, Sleath et al., 1999, Stevenson et al., 2004, Webb et al., 2001, Alexander et al., 2006, Noble, 1998). Provider-patient communication can influence adherence through influencing patients' knowledge and understanding of their disease and

treatment, through influencing patients' beliefs and attitudes towards prescribed treatment regimen and through influencing patients' motivation to adhere to their treatment (Alexander et al., 2006). Nonetheless, effective communication can be challenging when working with special populations such as patients from diverse cultural backgrounds, patients with poor health literacy and elderly patients (Alexander et al., 2006). Finally, the importance of creating and maintaining good provider-patient relationship and communication has been highlighted in national guidelines on adherence and shared decision making (Nunes et al., DoH, 2010).

Patients' intention to adhere to medication may also be influenced by the kind of information given. For example, it is important to include clear information about both benefits and adverse effects of a prescribed medication to enhance patients' intentions to adhere (Bersellini and Berry, 2006). Furthermore, information such as risks about adverse effects has to be communicated in a fashion that patients understand (Berry et al., 2006). Another important factor to increase patient satisfaction with the consultation process is personalisation of information (Berry et al., 2003). However, there is no consistent evidence that written information, such as patient information leaflets, increase patient satisfaction or adherence to treatment (Raynor et al., 2007).

1.6.4 HEALTH CARE SYSTEM AND HEALTH POLICY

Health care systems and health policy can also create barriers for patients' adherence to medications through limiting access to health care, using a restricted formulary and imposing copayments or high costs for drugs (Elliott, 2009, Osterberg and Blaschke, 2005). Societal policies may also influence adherence through changing public demand for certain treatments, such as allowing or banning advertising prescription only drugs to potential patients. In addition, changing the supply of drugs may also influence adherence. For example, through deregulating prescription only drugs to over the counter drugs and allowing more HCPs, such as nurses and pharmacists, to prescribe drugs (Horne et al., 2005).

As already mentioned, health policy is changing all over the world to become more patient centred by aiming to increase patient participation in treatment decisions

and specifically promoting adherence as a priority (DoH, Nunes et al., 2009, WHO, 2003). It remains to be seen whether these initiatives will result in increased patient adherence to health care recommendations and whether the desired improvement in health outcomes will ensue.

This section has given an overview of factors associated with adherence and all are mainly related to being able to predict nonadherence (which is unreliable); with much less research having explored the patients' reasons why they are not taking their medication as prescribed. Qualitative research on patients' medicine taking has been synthesised by Pound et al (2005) and further updated and published in the NICE guidelines on adherence (Nunes et al., 2009). Pound et al. (2005) suggested a model for medicine taking where patients tend to fall into three groups: first, the passive accepters who accept their treatment without question and tend to adhere as prescribed; second, the rejecters who reject the treatment completely; third, the patients who have worries and concerns about their medicines. The third group is thought to either actively accept the treatment after evaluating it and thus tend to adhere or choose to modify the regimen and thus not adhere as prescribed (Pound et al., 2005).

Nonetheless, the factors that are (or are thought to be) associated with adherence have been incorporated into different theories that are meant to explain and predict health behaviour. In the following section these theories have been critically evaluated. The section will conclude by suggesting the advantage of using the Accident Causation Framework (ACF; Reason 1990) to further our understanding of nonadherent behaviours.

1.7 THEORIES USED IN ADHERENCE RESEARCH

Research should be anchored in earlier knowledge accumulated within the field with the aim of striving towards a coherent picture of the factors influencing adherence. To facilitate the research process, the utilization of theories explaining the health behaviour under investigation is essential. In addition, a sound theoretical base is essential when developing and evaluating behavioural change interventions as promoted by the Medical Research Council (MRC) guidelines for

developing complex interventions (Campbell et al., 2000, Craig et al., 2008). In addition, behavioural change theories can support the implementation of evidence based practice guidelines (Michie et al., 2005).

There are three terms that are generally used to refer to a body of knowledge developed to explain a phenomenon (including specific concepts and their interactions): theory, framework and model. Even though it might be possible to argue for semantic and philosophical differences in how these terms are (or should be) defined, it is of limited practical use to do so as these terms are used interchangeably by researchers and theorists alike. In this thesis I use these terms in the following manner (although I always refer to published theories / frameworks / models by their given name):

- Theory: refers to the structured body of knowledge that drive specific hypotheses about an outcome
- Framework: is a pictorial representation of the specific concepts and their interactions that are hypothesised to influence an outcome (extracted from the theory)
- Model: I only use 'model' to refer to theories that are named that way

Theories generally summarise the factors thought to influence the behaviour (e.g. cognitions, physical abilities, social influences and organisational structures) as well as the interaction of the different factors. The theory can then be used to generate research hypotheses of behavioural prediction or behavioural explanation. Subsequently, the different components of the theory, as well as the behaviour, are measured in participants. Ideally, if the results correspond to the study hypothesis the theory is supported, and if the results are not in accordance with the predictions the theory could be revised or refuted. Should the theory prove to accurately predict and explain behaviour, it can be implemented in the development of research methodologies, measurements and behavioural change interventions, as well as inform clinical practice.

However, although intervention studies arguably should be theory driven (Craig et al., 2008, Campbell et al., 2000), large quantities of intervention studies are not driven by theory (Haynes et al., 2005, Michie et al.) and it is widespread practice to

have entirely intuitive interventions (Elder et al., 1999). Even though some of these interventions lead to improved adherence for a limited time, they are often elaborate, multicomponent interventions that would be difficult and / or expensive to implement in practice.

Furthermore, in order to further enhance and develop better interventions it is important to understand *how* the intervention worked, not just *that* the intervention improved adherence. One reason for this is that unnecessary components of an intervention would simply increase the cost of the intervention without any associated benefit to increase adherence rates. Another reason is to find out whether it is possible to develop standardised interventions that will work over whole populations, or if it is necessary to tailor interventions to individual patients.

To investigate how the intervention worked a theoretical framework is essential to evaluate the results. Adherence interventions are often referred to as 'complex interventions', interventions where the 'active ingredient' is difficult to specify (Campbell et al., 2000, Craig et al., 2008). Take the example of a controlled medical trial in which a drug is tested against a placebo substance: with a presumed positive outcome and sound methods it is possible with some certainty to say that the drug was the active ingredient. In contrast, within an intervention to enhance adherence it is difficult to say with certainty what components of the intervention directly led to a change in behaviour. Naturally, even with theory-driven adherence research it is challenging to distinguish causal factors, as well as controlling for confounding variables; though in atheoretical adherence research it is virtually impossible.

Another theoretical challenge is that there is a range of competing theories used in the adherence research field, which makes it difficult to compare methods and results between studies of diverse theoretical bases. Therefore, a theory should ideally incorporate the full range of concepts found to influence nonadherence. The following section will critically evaluate the theories most commonly used in the adherence field. Attention is given to whether the theories can account for the range of factors that have been shown to influence intentional and unintentional

nonadherence; both in terms of patient specific factors, such as beliefs and dexterity, as well as recognising the influence of HCPs, the health care system and policy.

1.7.1 SOCIAL LEARNING/COGNITION THEORIES

The theories most frequently used in adherence research are derived from the social learning theory, later renamed social cognition theory, which combines features from cognitive psychology and behavioural psychology (Rotter, 1954). These theories are now generally referred to as social cognition theories (SCTs) or social cognition models (Bosworth and Voils, 2006). The SCTs share the basic assumption that behavioural intentions and ultimately behaviour are largely determined by beliefs and attitudes. This section will discuss the theories that have been identified as having acquired the most empirical support within the research field of adherence (Bosworth and Voils, 2006). The theories related to the social learning traditions share their main limitations in explaining and predicting nonadherence. These shared limitations will therefore be discussed in-depth in section 1.7.2 on limitations and weaknesses of SCTs.

The two theories used in adherence research that are closest to the original social learning traditions that will be discussed are:

1) Locus of control theory (Rotter, 1954, Rotter, 1966, Wallston, 1992)
2) Self-efficacy (Bandura, 1986).

In addition, the following theories derived from social learning traditions will be discussed:

3) The health belief model (Rosenstock, 1974, Rosenstock et al., 1988)
4) The theory of reasoned action (Ajzen and Fishbein, 1980) and the theory of planned behaviour (Ajzen, 1985, 1991),
5) The protection motivation theory (Rogers, 1975, Rogers et al., 1983)
6) The self-regulatory model of illness (Leventhal et al., 1992)
7) The transtheoretical model (Prochaska and DiClemente, 1983)

1.7.1.1 LOCUS OF CONTROL THEORY

Locus of control theory was originally developed by Rotter (Rotter, 1954, Rotter, 1966) and is an attempt to explain why different people learn very different things when provided with the same information. Some individuals respond to reinforcement by being more likely to repeat a behaviour that has been rewarded and less likely to repeat a behaviour that has been punished. Yet other individuals do not respond in the same manner, their behaviour seems more irrational as if they believe their behaviour does not significantly influence the outcome.

According to the locus of control theory this difference depends on a factor called 'locus of control', which has two dimensions: internal and external locus of control. Accordingly, individuals high on internal locus of control believe the reinforcement is contingent on their behaviour and are thus considered to be more likely to engage in the behaviour, whilst individuals high on external locus of control believe reinforcement is contingent on external variables, such as chance, luck or fate and are thus considered less likely than the internals to engage in the behaviour.

Initially having been a unidimensional theory with internal and external locus of control at the extremes, the theory was later made multidimensional by dividing the 'external' concept into control by 'powerful others' (such as health providers) and control by 'chance' (Levenson, 1973). These three orthogonal dimensions were subsequently applied to health behaviour, and operationalised with the multidimensional health locus of control scale (Wallston et al., 1978, Wallston et al.). Accordingly, on one extreme are individuals who believe their own actions are the most important determinant of their health status and are again thought more likely to engage in health promoting behaviour. On the second extreme are the individuals who believe their health is contingent on chance, luck or faith; and on the third extreme are individuals who rely on powerful others, such as health care providers, for reinforcement to maintain their health behaviour. The people scoring high on external locus of control on either of these two external dimensions of the multidimensional health locus of control scale are considered less likely than the internals to engage in the health behaviour.

Although some studies have found a positive association between individuals scoring high on the internal locus of control dimension and adherence to medication in hypertension (Kirscht and Rosenstock, 1977), HIV (Molassiotis et al., 2002) and diabetes (O'Hea et al., 2005), other studies have found no association between locus of control and treatment adherence (Schapira et al., 1991). Generally, health locus of control scale is found to be a weak predictor of adherence and only accounts for about 10% of variance in health behaviour (Wallston, 1992). In essence locus of control refers to a person's perception that his/her behaviour can influence an outcome. However, others have argued that what determines whether the person then performs the behaviour is his/her confidence in being able to perform the behaviour. This is referred to as 'self-efficacy' and will be discussed in the following section.

1.7.1.2 SELF-EFFICACY

Self-efficacy originates from social cognitive theory and refers to the level of confidence an individual has about performing a certain behaviour (Bandura, 1977). Self-efficacy is a product of efficacy expectations, which is a person's perceptions of his/her ability to engage in a specific behaviour, and outcome efficacies, which are a person's evaluations of the outcomes of a specific behaviour. It is argued that a person with high efficacy expectations and high outcome efficacies is more likely to adhere to treatment. Self-efficacy is usually considered to be behaviour specific. For example, a person may show high self-efficacy to maintain a healthy diet, but may show low self-efficacy to continuously adhere to a prescribed medication.

Some findings suggest self-efficacy is positively associated with treatment adherence in for example hypertension (Roh, 2005), asthma (Saskia et al., 2002) and HIV (Molassiotis et al., 2002); whereas other studies did not find association between self-efficacy and treatment adherence (Chlebowy and Garvin, 2006). Research has shown that adding the component of self-efficacy beliefs to other SCTs, such as the health belief model, theory of reasoned action and protection motivation theory, increases the amount of variance of specific health behaviours the theory can account for (Schwarzer and Fuchs, 1996). Of course, it is not

surprising that a person who believes they can carry out a certain behaviour, and believes the behaviour will be effective in reaching a desired end, are more likely to actually do so than a person who believes they are incapable of carrying out the specific behaviour. However, such findings are influenced by general methodological limitations arising from how self-efficacy has been operationalised, which will be discussed in section 1.7.2.2 (pp. 60) on methodological limitations of the SCTs.

1.7.1.3 THE HEALTH BELIEFS MODEL

The health belief model (Figure 1) was developed specifically to predict and explain health related behaviours of why people fail to engage in behaviour that is generally considered to be 'good for them', such as failure to attend a screening or failure to exercise (Rosenstock, 1974). The theory's main components are a set of core beliefs that are assumed to influence the likelihood of the patient carrying out the required health behaviour.

In relation to adherence, the patient's beliefs that are thought to be relevant are, for example, beliefs about their own susceptibility to the illness; the severity of the illness; the costs of adhering to prescribed treatment (e.g. perceived side effects); and the benefits of adhering to the treatment (e.g. perceived management of illness). Accordingly, if the pros outweigh the cons of adhering to treatment adherence is the likely behavioural outcome.

The health belief model was further developed by Becker and Maimam (Becker and Maiman, 1975) who argued that in order for the patient to adhere to the prescribed treatment cues of action are also needed. The cues of action can be either internal (e.g. symptoms) or external (e.g. information).

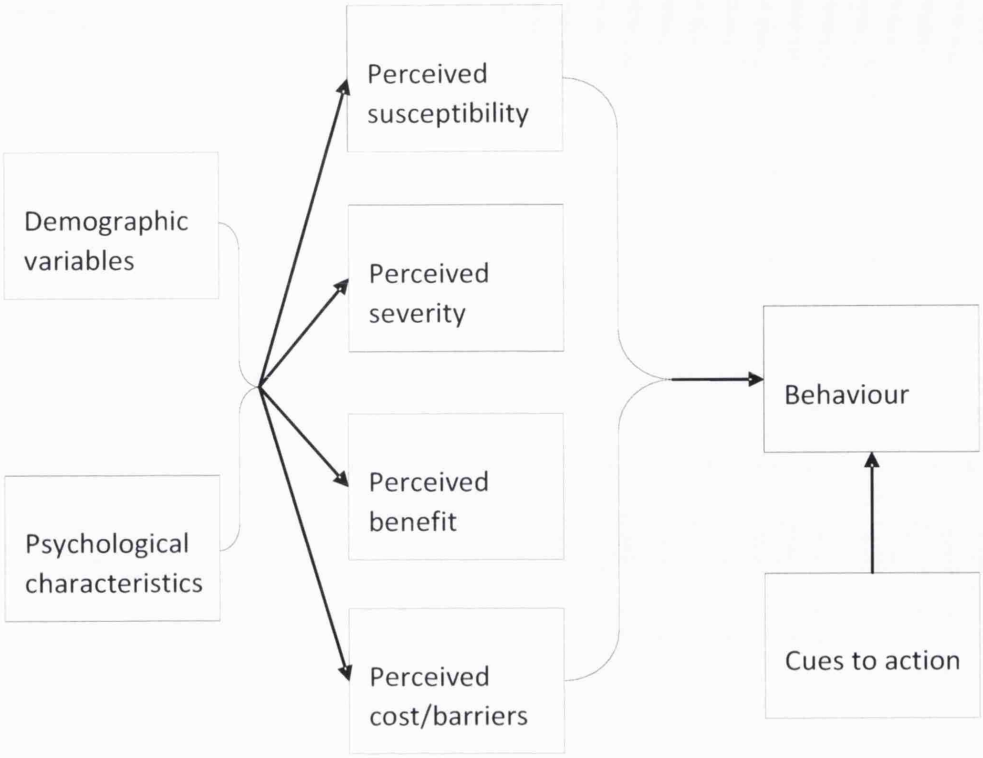

FIGURE 1 HEALTH BELIEF MODEL, ADAPTED FROM BOSWORTH AND VOILS 2006

Later it was suggested that perceived control, similar to the construct of self efficacy, should be added to the theory, i.e. if the patient feels confident that they can adhere to their treatment it is more likely they will (Rosenstock et al., 1988). The health belief model has been used to predict adherence to treatment in a range of illness groups such as hypertension (Kirscht and Rosenstock, 1977), diabetes (Daniel and Messer, 2002) and renal disease (Cummings et al., 1982).

Two shortcomings of the health belief model are that it does not explain how perceived threat and the cost-benefit analysis are turned into action and does not take into account social influences on behaviour. The theory of reasoned action and the theory of planned behaviour, which will be discussed in the following section, are trying to address these two shortcomings by aiming to explain the relationship between thought and action.

1.7.1.4 THE THEORY OF REASONED ACTION AND THEORY OF PLANNED BEHAVIOUR

The theory of reasoned action (Figure 2) was developed by investigating the relationship between attitudes and behaviour (Fishbein and Ajzen, 1975, Ajzen and Fishbein, 1980). The fundamental tenets of the theory of reasoned action are that behaviour is preceded and predicted by the formation of intentions. Intentions, in turn, are determined by attitudes towards the behaviour, which are defined as the product of beliefs about the likely outcome and the perceived value of the outcome. Social influence is considered an important factor that affects health behaviour and is incorporated in the theory as 'subjective norms'; the individual's beliefs regarding others' views of the behaviour and the individual's motivation to support these views.

To improve the predictions of intentions and behaviour 'perceived behavioural control' were added to the theory of reasoned action to form the theory of planned behaviour (Ajzen, 1985, Ajzen, 1991). Consequently, the theory of planned behaviour is trying to explain that these perceptions can influence volitional behaviour (volitional behaviour is referring to the willpower to engage in the behaviour, beyond the intention to do so). For example, even though the patient intends to adhere he/she might engage in nonadherent behaviour because of perceived barriers that result in an inability to realise the intention into action. Perceived behavioural control is often likened to the concept of self-efficacy (Ajzen, 1991, Bandura, 1977). In essence the stronger a person's behavioural intentions are and the stronger perceived behavioural control the person has, the more likely the person is to perform the behaviour. The theories of reasoned action and planned behaviour have been used to predict adherence in for example hypertension (Miller et al., 1992) and malaria (Abraham et al., 1999).

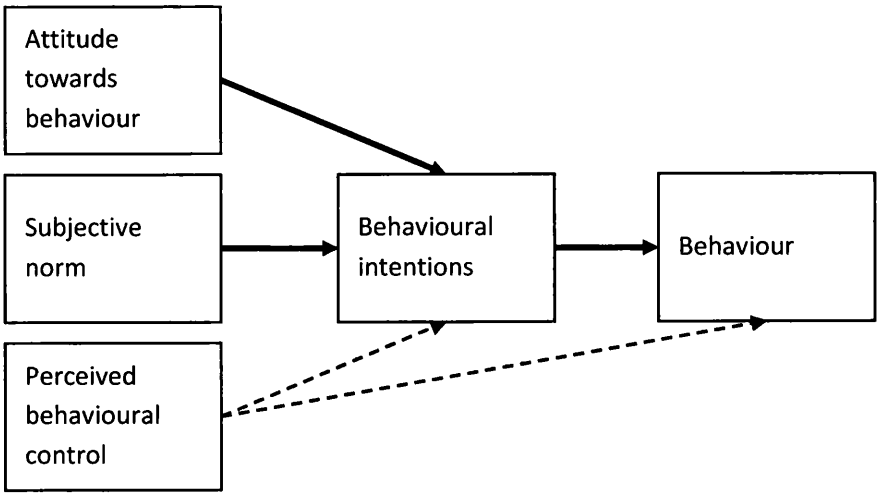

FIGURE 2 THEORIES OF REASONED ACTION (SOLID LINES) AND PLANNED BEHAVIOUR (DOTTED LINES), ADAPTED FROM BOSWORTH & VOILS 2006.

1.7.1.5 PROTECTION MOTIVATION THEORY

Originally, protection motivation theory (Figure 3) proposes that fear appeal (i.e. a message that uses fear to persuade) may lead to attitude change, which will ultimately result in behavioural change (Rogers, 1975, Rogers et al., 1983). The theory was later revised to a more general theory of cognitive change used to understand decision making in relation to health change (Rogers et al., 1983). Similar to theories of reasoned action and planned behaviour, the protection motivation theory assumes that behaviour is best predicted by behavioural intentions, which are labelled *protection motivations.*

In contrast to the theory of planned behaviour, which proposes that attitudes, social norms and perceived behavioural control influence behavioural intentions; protection motivation theory suggests threat and coping appraisals influence protection motivations. Threat appraisal refers to a value judgement of the components of a fear appeal that determines how personally threatened one feels. The threat appraisal incorporates perceived vulnerability, susceptibility to the threat, perceived severity, and fear arousal induced by the threat. Coping appraisal refers to the evaluation of the suggestions for coping with the threat and incorporate self-efficacy (how capable one feels to perform the behaviour),

response efficacy (beliefs about how effective the behaviour will be in reducing the threat) and response costs.

Protection motivation theory assumes that threat and coping appraisals are initiated by environmental (e.g. information, communication, observational learning) and intrapersonal (e.g. illness symptoms, personality, experiences) factors. According to the protection motivation theory, coping appraisal does not only have a direct influence on protection motivations, but may lead to maladaptive coping responses, which can influence protection motivations negatively. The protection motivation theory has been applied to explain adherence to treatment in for example diabetes (Palardy et al., 1998) and asthma (Bennett et al., 1998). The protection motivation theory shares similar constructs with the self-regulatory model of illness (Leventhal et al., 1992), discussed in the following section, although the active role of the patient in coping with the illness and treatment is more emphasised in the latter.

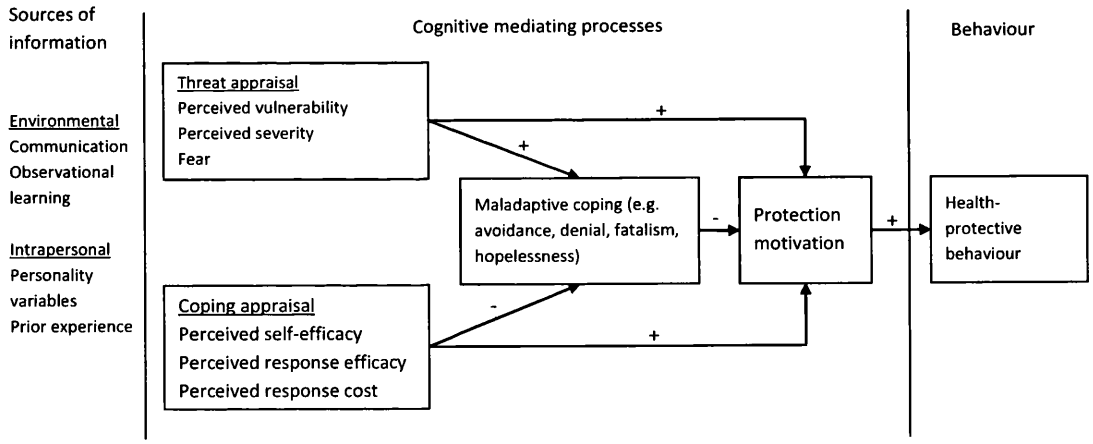

FIGURE 3 PROTECTION MOTIVATION THEORY, ADAPTED FROM BOSWORTH & VOILS 2006

1.7.1.6 SELF-REGULATORY MODEL OF ILLNESS

The self-regulatory model of illness (Figure 4) assumes that the patient is an active problem solver (Leventhal et al., 1992). Health threats, such as illness, are seen as problems that the patient will try to solve through health-related behaviours. Health-related behaviour would thus be the attempt to close the gap between the current health status and a future goal state. Patients' health-related behaviours

may be diverse depending on their interpretations and evaluations of their illness. Adherence and nonadherence are health related behaviours adapted to cope with the illness as it is perceived by the patient. Responses to illness are suggested to follow three broad stages.

1) Cognitive and emotional representations of the illness according to the perception of internal cues (e.g. symptoms) and external cues (e.g. information).
2) Development and implementation of a coping plan to deal with the illness
3) Appraisal of the coping plan

These three processing stages are thought to operate in parallel on both a cognitive and an emotional level. However, the theory suggests there are dynamic interactions between all the different processing levels and the perceived outcome of the coping plan may influence the representation of the illness. The self-regulatory model is similar to the SCTs in that it focuses on cognitive representations of the illness as an essential determinant of health related behaviour. In contrast to the other SCTs and the transtheoretical model (discussed below), the self-regulatory model emphasises the coping appraisal process and how this process influences cognition, emotion and behaviour. However, the emotional component of the self-regulatory model of illness has rarely been operationalised in adherence research.

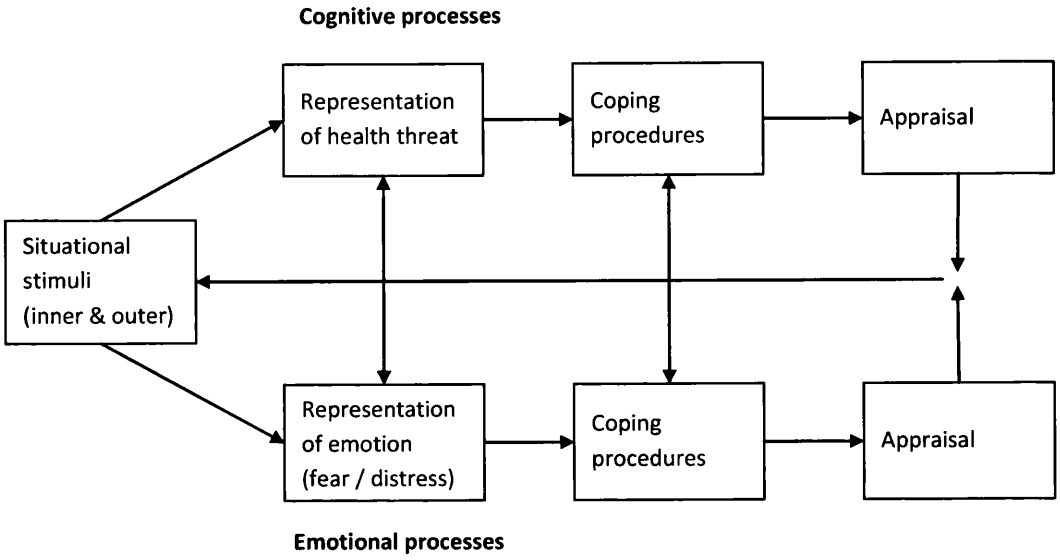

FIGURE 4 SELF-REGULATORY MODEL OF ILLNESS, ADAPTED FROM LEVENTHAL, DIEFENBACK & LEVENTHAL, 1992

The cognitive level of the self-regulatory model, on the other hand, was operationalised through the illness perception questionnaire (Weinman et al., 1996). The illness perceptions questionnaire comprises of five scales thought to represent the patients' cognitive representations of illness:

- Identity: symptoms associated with the illness
- Cause: personal ideas about aetiology
- Timeline: perceived duration of illness
- Consequences: expected effects and outcome
- Cure control: how to control or recover from the illness

Illness perceptions have been shown to be associated with adherence to, for example, asthma treatment (Jessop and Rutter, 2003) and hypertension (Chen et al., 2009).

Clearly patients must have cognitions and beliefs relating to their treatment, as well as relating to their illness. Beliefs about treatment have been found to be associated with treatment adherence and can be subdivided into specific beliefs, which are defined as beliefs related to the individual patients' treatment, and

general beliefs, defined as peoples' ideas about medicines in general (Horne et al., 1999).

In line with the finding that treatment related beliefs directly influence adherence, the necessity-concerns framework was presented as an attempt to operationalise parts of the cognitive constructs of the self-regulatory model (Horne et al., 1999). A study that used a cross section of chronic illnesses found that patients specific beliefs about their treatment can be grouped under two core beliefs, necessity beliefs and concerns (Horne et al., 1999). Necessity beliefs refers to the patient beliefs about whether their treatment is necessary for controlling their illness, i.e. taking my medicines as prescribed is necessary. Concerns refer to the patient's concerns regarding adverse effect of the treatment, such as side effects or dependency. Patients are thus thought to engage in an implicit cost-benefit assessment, weighing the necessity of treatment against the related concerns, which influence the decision of whether to adhere to the treatment or not. Using the necessity-concerns framework to assess beliefs about treatment accounted for 19% of the explained variance in adherence and was a more powerful predictor of adherence behaviour than clinical and demographic factors (Horne et al., 1999).

However, explaining 19% of the variance is still just a modest amount of the total variance in behaviour. The limited explanatory power of the necessity concerns framework may be because the emotional constructs of the self-regulatory model have not been operationalised in parallel. In addition, the necessity concerns framework assumes that all nonadherent patients are engaging in this behaviour intentionally, although a large proportion of patients are likely to be unintentional nonadherent. Had the framework been used to predict only intentional nonadherence it is possible a larger part of the variance in behaviour could have been accounted for.

The self-regulatory model can explain patient's change in health related cognitions and emotions through the feedback loop from appraisal of the coping procedures influence on current health status (situational stimuli). This is similar to the transtheoretical model, which tries to specifically explain the dynamics of how health related cognitions may change over time.

1.7.1.7 THE TRANSTHEORETICAL MODEL

The SCTs cannot fully operationalise the notion that individuals' health related cognitions may change over time. In response to this the transtheoretical model (Figure 5) focuses on the process of behavioural change through different stages; each stage is associated with specific cognitions (Diclemente et al., 1991, Prochaska and DiClemente, 1983). The transtheoretical model describes 5 such stages:

1. Precontemplation: the person has no intention of changing their behaviour;
2. Contemplation: the person is considering change;
3. Preparation: the person starts to make small changes and makes plans for how to make these changes;
4. Action: the person is engaging in changed behaviour;
5. Maintenance: the person has sustained the changed behaviour over time, often defined with the prerequisite that the changed behaviour need to be maintained for more than 6 months.

The progression through the different stages is not necessarily linear from 1 to 5. The movement can be dynamic; either regressing to earlier stages at anytime or omitting stages. For example, a person might have reached the maintenance stage, then revert back to the contemplation stage and finally go directly to the action stage without need for the preparation stage the second time around.

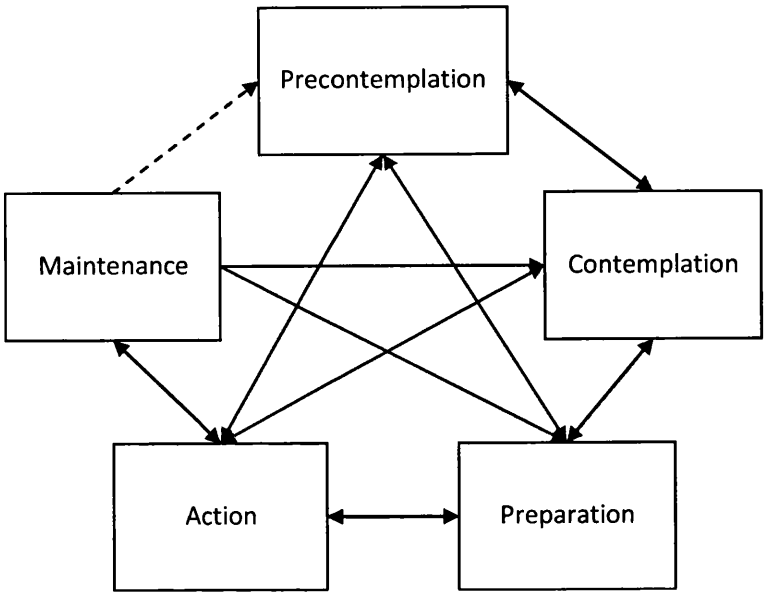

FIGURE 5 TRANSTHEORETICAL MODEL (DICLEMENTE, ET AL., 1991; PROCHASKA & DICLEMENTE, 1983)

The transtheoretical model incorporates a rational decision-making process of weighing perceived pros and cons of adopting certain health behaviour such as adhering to treatment. According to this theory, a person's perception of pros and cons of behaviour may vary across the different stages of change. Accordingly, the cons of adopting a new behaviour are assumed to outweigh the pros in the precontemplation stage. Subsequently, as the person progresses through the different stages, the pros of adopting health behaviour are thought to outweigh the cons. Similarly, the cons may be perceived as overbearing as the person reaches a particular stage of change, which may lead to regression to an earlier stage. For example, the unpleasant side effects of highly active antiretroviral therapy may make a patient regress to an earlier stage of nonadherence.

An advantage with using the stages of change theories when developing interventions is that it may be possible to identify which stage the patient is at, thus the intervention can be more specifically target at the patient's needs. However, one of the major criticisms of the theory is that there is no explanation for what processes actually help progress behavioural change between the stages.

The theory has been used extensively in research into health related behaviours such as smoking (Anatchkova et al., 2007, Hoeppner et al., 2006, Ruggiero et al.,

1997), contraceptive use (Peipert et al., 2007) and exercise (Marcus et al., 1996, Marcus and Simkin, 1994). In comparison, the theory has rarely been used in medication adherence research, with its first application in this area reported in 2000 (Willey et al., 2000).

1.7.1.8 SUMMARY OF SOCIAL COGNITION THEORIES

In summary, the SCTs share the assumption that peoples' beliefs and cognitions directly influence intentions to adhere to treatment, as well as actual adherent behaviours. According to these theories behavioural change can be achieved by influencing people's beliefs and cognitions related to adherence through interventions. Whilst the SCTs focus on static behaviours, the dynamic process of behaviour and the continuous interaction between cognitions and behaviour are central to the self-regulatory model of illness and the transtheoretical model. In addition, self-efficacy has been found to be influential in changing and maintaining health behaviours and is often added to existing theories in order to increase the amount of explained variance in adherence. The SCTs have together generated many hypotheses, research and interventions, some better and some worse than others, and they can thus be considered to have been useful theories within the field of adherence research (Ogden, 2003). Nevertheless, all the existing theories can only account for modest proportions of the variance in adherence, and a range of limitations and weaknesses have been exposed, which will be discussed in the following section.

1.7.2 LIMITATIONS AND WEAKNESSES OF SOCIAL COGNITION THEORIES

There are a range of criticisms of the social learning/cognition theories. The three most prominent limitations of the social cognition theories are:

1) The assumption that behaviour is rational and largely determined by weighing pros and cons of performing a certain behaviour, which means the theories cannot account for non-rational behaviour.

2) The SCTs can also only account for intentional nonadherence and not account for unintentional nonadherence, which accounts for a considerable proportion of nonadherent behaviour, as was discussed in section 1.3.1.

3) None of the theories explain the interaction of the health care system on patient's adherence (Bosworth and Voils, 2006).

These limitations and more will be discussed in the following sections, which are divided into conceptual limitations, methodological limitations and predictive limitations of the SCTs.

1.7.2.1 CONCEPTUAL LIMITATIONS

The most notable conceptual limitations of the SCTs are that they can neither account for irrational behaviour (Horne and Weinman, 1998) nor for unintentional nonadherence or health care system influences on adherence (Bosworth and Voils, 2006). These are three imperative conceptual weaknesses as patients often seem to behave non-rationally, large proportions of nonadherers engaging in this behaviour unintentionally and health care system influences on behaviour have been shown (e.g. through medicine co-payments).

The SCTs, including the health belief model, the theories of reasoned action and planned behaviour, the protection motivation theory and the social cognitive theory, are based on the assumption that adherent behaviour is contingent on a rational decision making process of weighing the pros and cons of adhering to treatment or not (Conner and Norman, 2005). The cost-benefit concept can be considered useful as an organising frame for different cognitions that may influence adherence, but has limited predictive value (Bosworth and Voils, 2006). Furthermore, this assumption has been criticised as it does not provide an adequate description of the way patients make treatment decisions (Frisch and Clemen, 1994). In addition, it is unlikely patients are integrating information in such a rational way, possibly except for the most important treatment decisions such as when deciding on which cancer therapy to initiate or decisions regarding major surgery.

The SCTs have been criticised for only accounting for the concept of intentional nonadherent behaviour and not unintentional nonadherence. As was discussed in section 1.3.1, research has show that within populations of nonadherent individuals the frequency of unintentional nonadherence is often found to be higher than intentional nonadherence (Clifford et al., 2008, Atkins and Fallowfield, 2006, Lowry et al., 2005, Wroe and Thomas, 2003). However, it is not the fact that the theories only can account for intentional behaviour per se that is the problem, if nonadherent behaviours were dichotomised and the theories were only applied to predict behaviour in the proportion of participants who were intentionally nonadherent there would be less grounds for criticism.

However, the SCTs are generally applied to populations of nonadherent patients without controlling for this dichotomy. Therefore, it is not surprising the theories fail to account for large proportions of the variance in adherence behaviour. Clearly it would be useful for a theoretical framework to be used in adherence research and clinical practice to distinguish between intentional and unintentional nonadherence, as well as incorporate factors influencing nonadherent behaviour, whether intentional or not. This differentiation between intentional and unintentional nonadherence may be pivotal in developing effective interventions to enhance adherence (WHO, Balkrishnan, 2005, Barber et al., 2005).

As discussed in section 1.6.3 and 1.6.4 adherence to treatment can also be influenced by health care system factors such as health care provider – patient interaction, organisational structures and health policy. The SCTs share a major limitation in that they cannot explain the influence of any such concepts on individual patients' adherence behaviour (Bosworth and Voils, 2006).

Further concern over conceptual limitations have been raised over the fact that when results are obtained that are not supporting a specific theory these results are rarely used to refute the theory; instead, explanations for why the results are flawed, and how the theory can still be upheld are offered (Ogden, 2003, Chalmers, 1999). Ogden further criticised the tendency to add more and more constructs to existing theories in attempts to account for a larger part of the variance in treatment adherence (Ogden, 2003). According to Ogden these tendencies create

theories that become less and less testable by hindering the theory's ability to generate refutable hypotheses, thus obstructing the advancement of theory and ultimately delaying clinical applications (Ogden, 2003). These arguments are based on a strict Popperian view of advancing scientific theory through falsification (see e.g. Popper, 1989)

However, these arguments can be challenged on the basis that theoretical development often involves updating and enhancing constructs within a theory as well as the associated research methods and measurements (Lakatos, 1970). We are constantly integrating previous knowledge and new discoveries to better explain and predict an event. It is likely to hamper scientific progress if previous theory should simply be refuted when hypothesis are not supported, in particular considering the possibilities of type II errors. Indeed, a theory can arguably only be refuted if it has been tested against another theory that has proven to be superior in explaining a specific event (Lakatos, 1970).

When considering testing the SCTs against each other it becomes evident that many of the theories' components are overlapping (Table 1). These overlapping constructs have led researchers to suggest that rather than test the theories against each other we should focus research on integrating theoretical concepts with the aim to increase the amount of variance that can be explained by the theories (Conner and Norman, 2005). This would be particularly useful when developing adherence enhancing interventions (Bosworth and Voils, 2006) as research has shown that the more successful interventions often are eclectic, targeting a range of diverse factors that are thought to affect nonadherent behaviour (Haynes et al., 2008).

However, even though eclectic interventions are more successful, it is not advisable to simply 'pick and mix' components that have shown to account for significant parts of the variance in studies of diverse theoretical basis, thus creating a novel 'integrated' framework. All components of a theory have been validated within that specific theory and should thereafter be operationalised within that theory. A novel theory consisting of previously validated constructs originating from diverse theoretical backgrounds has to be tested as a complete

theory before being implemented in applied research and intervention development.

Finally, the main problems with the SCTs remain even after considering creating an integrated social cognition theory using the constructs that account for the largest amount of variance in behaviour. That is, none of the existing SCTs can explain unintentional nonadherence or incorporate the broad range of factors discussed in section 1.6 that have been found to affect adherence, such as memory, dexterity, communication and organisational factors. In addition, even within specific frameworks, constructs labelled as different have often been operationalised very similarly. This is a major limitation which will be discussed further in the following section on methodological limitations of the SCTs.

TABLE 1 OVERLAPPING THEORETICAL CONSTRUCTS BETWEEN THE SOCIAL COGNITION THEORIES

	THEORETICAL CONSTRUCTS										
THEORY	Locus of control	Self-efficacy / perceived behavioural control	Severity / susceptibility	Behavioural intentions	Rational cost-benefit analysis	Perceived barriers / consequences	Cues for action	Perceived benefits / consequences	Subjective norm	Emotional representation /fear	Change in cognitions over time
The locus of control theory	✓										
Self-efficacy		✓			✓ (outcome efficacies)	✓					
The health belief model		✓ (added 1988)	✓		✓	✓	✓	✓			
The theories of reasoned action & planned behaviour		✓		✓	✓			✓	✓		
Protection motivation theory		✓	✓	✓	✓	✓		✓ (response efficacy)		✓	✓
Self-regulatory model of illness			✓		✓			✓ (appraisal)		✓	✓
Necessity concerns framework					✓	✓		✓			
The transtheoretical model		✓		✓	✓	✓		✓			✓

1.7.2.2 METHODOLOGICAL LIMITATIONS

Methodological limitations of the social cognition theories are mainly related to how the theories' constructs are defined and operationalised. It has been noted by several authors that many constructs between theories are labelled as different, but the underlying constructs seem very similar (Patino et al., 2005, Cummings et al.). In a review paper criticising the SCTs Ogden (2003) further highlights that many cognitive constructs, both within and between theories, are defined as different yet operationalised in very similar ways. In Ogden's review most of the studies tested the theory by correlating the theory's constructs with the intentions to perform the behaviour. One of the examples Ogden (2003) brings up is Lugoe and Rise (Lugoe and Rise, 1999), which correlated perceived behavioural control measured with the statement "How certain are you that you would be able to use a condom at the next intercourse?", with behavioural intention operationalised as "I intend to use a condom at the next intercourse". That similar statements like these correlate is hardly surprising.

Ogden refers to these as analytic truths, where the correlation found is created by the definitions and operationlisations of the constructs instead of by true exploration of the concepts (synthetic truth). The analytic/synthetic dichotomy was first introduced by Emanuel Kant in Critique of Pure Reason in 1781 (Kemp Smith, 1933) to distinguish between analytic propositions that are true by definitions (all bachelors are unmarried) and synthetic propositions that are not true by simply definitions, but that will have to be researched (all bachelors are unhappy). To control for such pseudo correlations intra-correlations between scales' subsections should be performed. However, few papers present such information (Ogden, 2003).

To assess the influence cognitive constructs have on a specific behaviour, the behaviour itself must be measured. Unfortunately, research suggests that measurements based on SCTs may directly influence, even create, individuals' cognitions and beliefs relating to the specific behaviour under investigation (Bosworth and Voils, 2006). Consequently, associations found between the theoretical constructs tested and the intended behaviour may not be due to real

relations, but would have been created by the instrument used. The way the operationalised constructs of the SCTs may create cognitions and influence behaviour under investigation to is one of Ogden's (2003) primary criticisms.

Finally, the SCTs have rarely been tested against each other to test the relative predictive power of different theories (Bosworth and Voils, 2006). The following section will closer examine predictive limitations of the SCTs.

1.7.2.3 PREDICTIVE LIMITATIONS

Research indicates that the theories used within adherence research account for very modest proportions of the variance in both intention to adhere and actual adherent behaviour. This highlights the limited predictive power of these theories. For example, a review of the predictive and explanatory power of the theories of reasoned action and planned behaviour on behavioural intentions and health behaviour showed that the theories accounted for an average of 40% and 50% of variance in intention, and between 19% - 38% of the variance in behaviour (Sutton, 1998). Evidently, there is a clear gap between intention to perform a behaviour and actual behaviour; an area that is relatively under researched.

The relationship between intentions and behaviour is thus far from perfect and it has been suggested that past behaviour, rather than cognitions, may be a better predictor of current and future behaviour, i.e. a patient who has been adhering to prescribed treatment in the past is likely to keep doing so (Ogden, 2004). Research has been conducted to investigate the influence of past behaviour on health related behaviours such as breast self-examination (Hodgkins and Orbell, 1998), binge-drinking (Norman and Conner, 2006) and healthy eating (Conner et al., 2002). Past behaviour has also been shown to be a stronger predictor of adherence to immunosuppressant therapy in renal transplant patients than attitudes, subjective norms and perceived behavioural control and to account for 23% of variance of adherence behaviour (Chisholm et al., 2007). This study highlights the importance of recognising the influence of past behaviour when predicting adherence and implies that learning/experience is influencing behaviour. It could be seen as an obvious statement, but it is useful when assessing patients at risk for

nonadherence. Of course, it is important to recognise that adherence is circumstantial and treatment specific, which means that a patient's adherence to one medication or part of a treatment regimen might not necessarily mean they would adhere to a different medication or a different part of their regimen.

In summary, even though the SCTs generate an abundance of research and interventions the theories suffer from poor definitions and weak predictive power. However, research has shown that constructs shared by the SCTs explain modest amounts of the variance in behaviour. Therefore, research is needed to investigate the possibility of a theory that can incorporate these constructs and address the primary weaknesses by being able to explain unintentional and non-rational behaviour, as well as system influences on adherence behaviours. Consequently, we may be able to develop theory that explains more of the variance in behaviour, which can be used to drive future adherence research and intervention development. The following section will review three theories that have tried to address the limitations of the SCTs in explaining and predicting adherence to treatment.

1.7.3 THEORIES THAT ADDRESS LIMITATIONS OF THE SOCIAL COGNITION THEORIES

The limitations of the social cognition theories are primarily the theories' inability to account for unintentional nonadherence as well as system influences on individual patients' adherence to treatment. Recent studies with the objective to investigate the differences between intentional and unintentional nonadherence have seen theories derived from such diverse theoretical disciplines as economy and human error and safety research.

1.7.3.1 THE UTILITY THEORY

Wroe (2002) investigated intentional and unintentional nonadherence within the framework of utility theory derived from the fields of economy and game theory (Von Neumann and Morgenstern, 1947). Wroe (2002) operationalised the utility theory through the concept of the rational cost-benefit calculation also central to

many of the SCTs, but the results explained larger parts of the variance (40%) than the SCTs normally are found to do. This might be due to the fact that Wroe (2002) differentiated between intentional and unintentional nonadherence and only used the cost-benefit constructs to account for variance in intentional nonadherence.

However, unintentional nonadherence was not explained by the utility theory's central cost-benefit analysis. Furthermore, the definition of unintentional nonadherence was simply 'forgetting', thus unintentional nonadherence due to any other factors, such as problems with dexterity or misunderstanding of instructions, was not captured.

Finally, using the utility theory to predict behaviour is in a sense taking a step back in time (or in scientific progress?) to theories of behavioural prediction that predated the development of the SCTs (Conner and Norman, 2005). The SCTs in fact originate from theories explaining behaviour as directed by elaborate, although subjective, cost benefit analysis of the outcomes of performing a certain behaviour, such as expectancy-value theory (Peak, 1955) and subjective expected utility theory (Edwards, 1954). Of course these early theories have never been tested in explaining medication adherence, and to operationalise these theories now may give some insight into adherence behaviour that has been lost through the development of new theories. It may be more likely, however, that further developing the utility theory in the area of adherence will bring the utility theory into closer proximity to the theoretical basis of the SCTs; they would after all be likely to follow the same developmental path.

1.7.3.2 THE PERCEPTIONS AND PRACTICALITIES MODEL OF ADHERENCE

Another attempt to explain intentional and unintentional nonadherence was the perceptions and practicalities model (Figure 6), presented in a report for the National Co-ordinating Centre for NHS Service Delivery and Organisation (Horne et al., 2005). According to this approach unintentional nonadherence is caused by barriers to the patients' abilities to adhere to medication. Intentional nonadherence, on the other hand, is thought to be influenced by patients' beliefs and cognitions, thus the barriers facing intentional nonadherers would be

perceptual. The approach also recognises that many intentional and unintentional factors might be related. For example, a patient who does not consider a particular medication as important may be more prone to forget to take that medication.

Although the model show some promise in being able to explain both intentional and unintentional nonadherence, the approach's ability to explain nonadherence has not yet been explored and the constructs have not yet been operationalised or tested. Basically, the approach seems to provide a summary of factors that are already known to cause nonadherence. In addition, the capacity and resource limitations that are referred to are all patient specific, including memory difficulties, dexterity and problems with knowledge, and there is no reference to barriers created by the organisation of the health care system.

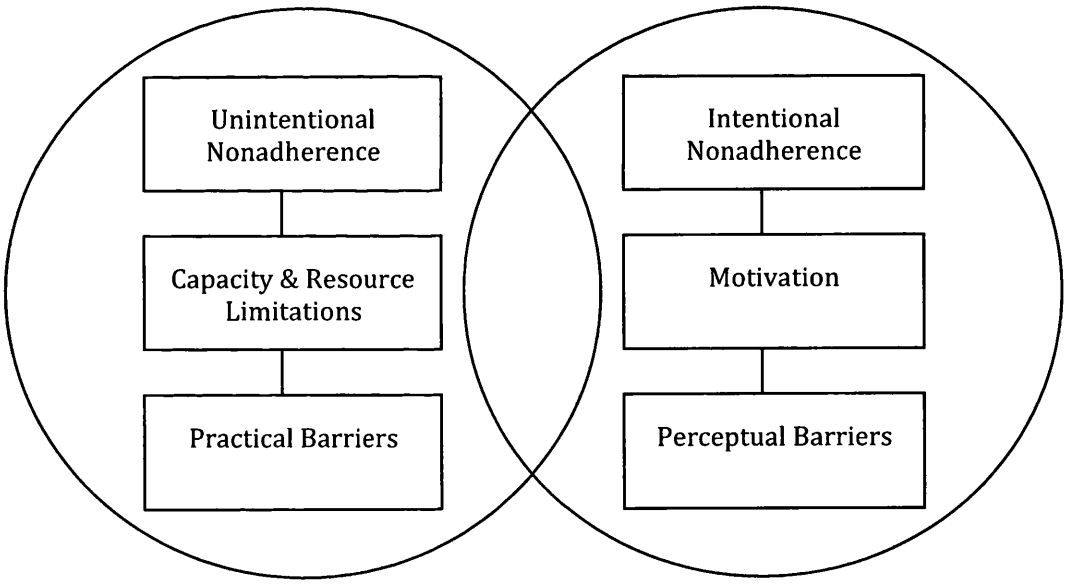

FIGURE 6 THE PERCEPTION AND PRACICALITIES MODEL TO UNDERSTANDING NONADHERENCE. ADAPTED FROM HORNE ET AL. 2005

1.7.3.3 THE ACCIDENT CAUSATION FRAMEWORK

The SCTs can explain intentional nonadherence through the influence of cognitions, attitudes and beliefs on adherence. However, as quoted by James Reason who developed the Accident Causation Framework (ACF):

> ...Attitudes and beliefs leading to non-compliance are only half the problem... [Reason 2008, pp. 58]

The current challenge within adherence research is to develop theory that can account for intentional and unintentional nonadherence as well as integrate factors influencing adherence from all levels of the health care process, from structural factors within the health care system and environmental factors, through communication and social influences, to specific cognitions and physical hindrances. The adaptation of the ACF (Reason, 1990) to explain adherence to understand nonadherent behaviour may be a step closer to realising this aspiration.

The ACF is the framework most widely used to explain medication errors, and in 2002 Barber suggested that we can further our understanding of patients nonadherence to medication by considering nonadherence a medical error; that patient's 'erroneous self-administration' was very similar to, for example, a nurse's 'erroneous administration'. In contrast to all the other theories that have been discussed previously in this introduction, the ACF explains intentional and unintentional failures to perform an action (such as adhering to treatment) through the influence of organisational factors within the health care system as well as individual patients' cognitions, attention and memory.

Preliminary research investigating the Accident Causation Framework's usefulness in explaining intentional and unintentional nonadherence to medication found that the framework adequately explained unintentional nonadherence but was less useful in explaining intentional nonadherence (Barber et al., 2005). However, it was concluded that further research is needed to adapt the ACF and the terminology specifically to adherence before the usefulness of the framework can be fully evaluated (Barber et al., 2005).

Within the field of oral anticancer drugs there has evolved an overlap between medication errors and patients' nonadherence (erroneous self-administration) to these drugs. This overlap is, for example, evident in the language used to refer to the patients' medication taking behaviour as 'administering' these drugs, instead of 'adhering to'. There is also a shift to focusing on the wider system surrounding the patient to explain problems with self-administration of oral anticancer drugs (Birner et al., 2006, BOPA, 2004, NPSA, 2008). This overlap may have arisen due to

the severe consequences of over dosing of these drugs can have, including death (Birner et al., 2006). In section 1.9, I will show that under dosing (i.e. missing doses) of these drugs also has severe consequences to patients' health. This shift towards referring to nonadherence to oral anticancer drugs as errors due to the safety issues surrounding patient self-administration of oral anticancer drugs further strengthen the argument for using theory derived from the human error field to understand nonadherence to medication. The prospect of using the ACF to explain nonadherence is promising and will be discussed in-depth in chapter 3.

Theories support our understanding of how behaviour can be explained, predicted and influenced. However, to evaluate whether predictions made and interventions designed on the basis of a particular theory have the desired influence on adherence behaviour we need to be able to accurately measure behaviour. There are many different measurements methods that aim to do just that and these different methods will be discussed below.

1.8 ADHERENCE MEASUREMENTS: DEFINITIONS, ASSESSMENTS AND METHODS

In research and practice a range of different methods and definitions have been used to operationalise adherence and nonadherence, which is one of the primary obstacles to synthesise the literature. In the following section I will explore how definitions and the way adherence is operationalised can influence the measurement methods used.

1.8.1 OPERATIONAL DEFINITIONS OF ADHERENCE

Measurements are closely linked with the definition of adherence/nonadherence. However, there is no universal standard definition or criteria of adherence/nonadherence thus the definitions used in research and practice vary depending on what particular nonadherent behaviour is being investigated and how the adherent behaviour is measured. It is common that studies use two definitions; one theoretical definition, for example the commonly used 2003 WHO definition that adherence is "the extent to which a person's behaviour corresponds

with agreed recommendations of a healthcare provider"; and one operational definition that is directly linked to the measurement, e.g. "the patient is nonadherent if 20% or more doses are missed as measured by pill count".

The reason why studies need an operational definition is that the theoretical definitions (in this example WHO 2003) tend not to give any direction of how to quantify adherence. The WHO definition has one more complication in that it implies that not only do you need to measure the extent to which a patient follows health care recommendations, but you also need to measure whether the patient initially agreed to these recommendations. This suggests that the patients should be considered adherent even if not taking their medication as prescribed as long as they did not agree with the prescribed treatment in the first place. However, what about if the patient only silently did not agree and never told the clinician? The complications of using broad theoretical definitions when aiming to measure nonadherence are evident. Indeed, to the best of my knowledge there are no studies using the 2003 WHO definition that have measured whether the patients' initially agreed with their health care recommendations or not.

In contrast to the theoretical definition, the operational definitions are rationally related to the research question under investigation, the components of nonadherent behaviour to be quantified and the specific method of measurement to be used. Nonadherence is composed of a range of distinct behaviours. In relation to medical treatment, nonadherent behaviours include not redeeming prescriptions or refills, altering dosing or time line between doses, and discontinuing treatment completely. Nonadherence also describes not engaging in treatment relevant dietary and exercise regimes and other self-care activities (Nunes et al., 2009, WHO, 2003).

Another operational definition of adherence that has been used is to dichotomised adherent and nonadherent patients according to whether their adherence rate is above or beneath the mean or median adherence rate in their specific populations (Vermeire et al., 2001). This makes very little sense considering that specific populations may have high levels of nonadherence and the mean or median adherence rate may be well below a potentially dangerously low adherence rate.

Furthermore, as discussed in section 1.3.1 the importance of differentiating between intentional and unintentional nonadherence has now been recognised (Nunes et al., 2009, WHO, 2003). This means that the definitions used in research and practice also needs to define these differences, and thus, a measurement of adherence ideally should be able to differentiate between intentional and unintentional nonadherence.

Adherence measures can be divided into two categories depending on the out-put data it produces; a continuous scale measure or a categorical measure. A continuous scale measures adherence rate and is often expressed as the percent of doses that have been taken (or percent of doses not taken). A categorical measure simply categorises patients according to being either adherent or nonadherent. The continuous scales are superior as they can measure incremental changes in adherence rate, as well as measure changes in adherence rate over time both within patients and in populations. A categorical measure can either categorise patients according to a cut-off point or according to the absence or presence of certain behaviour (e.g. if a patients state to sometimes forget doses they are categorised as nonadherent).

The use of a cut-off point when measuring adherence has been criticised (Bosworth and Voils, 2006). This is mainly because the cut-off points are often arbitrary and not based on supporting literature. The most widely used arbitrary cut-off point is 80%, where patients who take 80% or less of their doses are considered nonadherent and the patients who take more than 80% are considered adherent (Bosworth and Voils, 2006). The 80% cut-off seem to be based in assumptions of dose response curves and of how many doses a patient can miss without a clinical impact. However, cut-off points should not be arbitrary and researchers have thus argued for defining and measuring nonadherent behaviour in relation to the therapeutic outcome of the prescribed treatment (Liu et al., 2001, Bangsberg et al., 2001).

Nonetheless, cut off-point are in themselves not necessary inappropriate, as it would depend on the aims and methods of individual studies. However, the limitation with categorical measures are that they cannot capture changes in

adherence rates that are not crossing the cut-off point; thus improvements or deterioration of adherence rates that do not cross the cut-off would not be recognised. For example, let's say patients who take less than 80% are considered nonadherent. Imagine that a patient who initially took 50% of the prescribed doses after an intervention took 75% of doses. That is a substantial increase in the adherence rate. Nevertheless, that patient would, according to a categorical adherence measure, be considered nonadherent both before and after the intervention and no change would be detected. A continuous measure, on the other hand, can be used both to monitor changes in adherence rates, as well as dichotomising patients into adherent and nonadherent groups when this is appropriate and cut-off points are supported by relevant literature.

As previously implied, operational definitions of adherence and nonadherence are closely linked to the validity of the measurement used to quantify the behaviour. In essence a measure can be reliable without being valid but cannot be valid without being reliable. Reliability is the consistency of the measurement score over time or across persons being tested, whilst validity is referring to whether a measurement is measuring what it is supposed to measure (Murphy and Davidshofer, 2005). How to assess validity, reliability, as well as diagnostic abilities of adherence measurements, will be described in-depth in chapter 4, when the development and pilot stages of a new self-report adherence measurement will be presented. Nonetheless, when measuring adherence and when assessing the validity of new measurements it is always useful to triangulate several different measurement methods. The following section will therefore introduce the different adherence measurements most commonly used in adherence research.

1.8.2 ADHERENCE MEASUREMENTS

Authors of adherence measurement reviews have a tendency for wanting to dichotomise adherence assessment methods into two distinct groups; sometimes called direct and indirect methods, sometimes called objective and subjective methods. However, what is considered direct and indirect/objective and subjective methods varies between authors (Lowry et al., Vermeire et al., Gordis, Farmer, Vik et al., 2004, DiMatteo). Because of this disparity, in addition to the fact that such dichotomy of assessment methods does not increase our understanding of the utility of the individual methods, the following overview will not dichotomise measurements but simply consider each individually. The measures that will be discussed are pill-counts, medical records (pharmacy refill and health claim data), measures of drug and drug metabolites in the body, measures of viral, biotic or cancerous presence in the body, electronic monitoring and self-report.

1.8.2.1 PILL COUNTS

Assessing adherence rate using pill count involves measuring the amount of medication the patient is dispensed at base line and then counting the left over medication at follow-up appointments. Pill count adherence rate is generally defined as:

$$Adherence\ rate = \frac{(number\ of\ pills\ dispenced - the\ pills\ returned)}{number\ of\ pills\ prescribed} \times 100$$

This equation reflects the percentage of medication presumed to have been ingested by the patient (Bosworth and Voils, 2006). Pill count has also been used to assess adherence to oral anticancer treatment (Noens et al., 2009, Waterhouse et al., 1993).

Pill count is an affordable and straightforward measurement of adherence and is, along with medical records and self-report, one of the most commonly used methods to measure adherence (DiMatteo, 2004b). In addition, pill count gives a continuous scale output, which is desirable when measuring adherence.

The primary limitation with using pill-count, in addition to being intrusive to the patient, is that there is no information on whether the pills were in fact ingested or not. Individuals may be removing pills without consuming them, biasing the measurement and leading to an overestimation of adherence. It is also possible that a patient has taken doses from other sources of previously unused pills, thus leading to underestimation of the adherence rate. It might, however, be possible to increase the validity of these measures by using unannounced pill counts. At least this is likely to reduce the chances of patient discarding pills before a visit, although it will not reduce chances of patient ingesting pills from other sources. In addition, pill count does not give any information about the reasons why the patients missed doses; a distinction which we know is important in understanding patient nonadherence.

1.8.2.2 MEDICAL RECORDS: PHARMACY REFILL RECORDS AND HEALTH CLAIMS RECORDS

Data related to nonadherence can be obtained from medical records, such as pharmacy refill records and health claims records. Adherence to treatment is estimated from pharmacy refill records by calculating the number of days within a time period during which the patient would have had filled prescriptions, i.e. the number of dispensed tablets over the number of days in the time period (Bosworth and Voils, 2006).

Medical records are useful and are some of the few practical methods – when technology allows capturing of this data – to measure adherence in large patient populations over long periods of time. The output data is continuous and can therefore be used to measure changes in adherence rate. In addition, medical records are unlikely to be biased by patients desire to appear adherent as the patients are often unaware that their records will later be used to estimate adherence (Ruddy et al., 2009). Pharmacy refill records have been used to assess nonadherence to oral anticancer treatments (Partridge et al., 2003, Barron et al., 2007, Partridge et al., 2008). Similarly, health claims records were used by one study to estimate adherence to the oral anticancer drug imatinib (Darkow et al., 2007).

However, the limitation with estimating nonadherence according to pharmacy refill or health claims records is that even though a prescription has been filled it does not necessarily mean that the patient has ingested the medication as prescribed, leading to overestimation of adherence. There may also be some overlap in refills so that the refill data is not accurate and as is the case with pill counts there is no information whether missed doses were due to intentional or unintentional reasons.

1.8.2.3 PHARMACOLOGICAL AND BIOLOGICAL MARKERS OF ADHERENCE

Adherence has been measured through monitoring pharmacological markers such as blood and serum levels of drug or drug metabolites (Bosworth and Voils, 2006). This method is used less frequently than self-report, pill-counts and medical records to assess adherence, but has been used in several studies on adherence to oral anticancer treatments (Levine et al., 1987, Richardson et al., 1988, Sadahiro et al., 2000); in particular in paediatric and adolescent populations (Smith et al., 1979, Lansky et al., 1983, Lennard et al., 1995, Lancaster et al., 1997, Tebbi et al., 1986, Tamaroff et al., 1992, Festa et al., 1992).

These methods of estimating nonadherence has the advantage that it can be used in populations such as children that may be less able to communicate through other methods and it is convenient if the monitoring is part of standard care. However, these methods are very intrusive if not part of standard care, it can be expensive (e.g. if samples need to be sent to external labs to be analysed) and accurate measures of serum and drug metabolites are only available for certain medications, e.g. imatinib used for CML and gastrointestinal stromal tumors, and prednisone, which is an immunosuppressant drug used in a range of different cancers (Ruddy et al., 2009).

Furthermore, there are a number of ways in which these assessments can be biased. The variability in pharmacological markers varies depending on individual differences in drug absorption, distribution, metabolism and excretion (Ruddy et al., 2009), which is also influenced by drug-drug interactions and diet (Berg and Arnsten, 2006). The serum levels can also be influenced by patient behaviour, for

example a patient who is normally nonadherent may ingest an increased dose of medication the days before an appointment so that serum levels are inflated and who thus will appear adherent.

In some illnesses there are intermediate biological markers of drug use that can be used to estimate adherence. For example, in patients with the human immunodeficiency virus (HIV) their plasma viral load (CD4 cell count) is related to the amount of drug ingested (as well as illness progression). However, viral load measures of adherence are limited by a lack of technologic standardisation and differences in interpretations of results (Berg and Arnsten, 2006). Furthermore, most oral anticancer drugs do not produce similar biological markers that can be measured in a clinical setting in order to estimate adherence to the prescribed treatment (Ruddy et al., 2009). However, imatinib used in CML constitute an exception as disease progress can be measured and has been associated with adherence, which will be explained in section 1.9.1.

1.8.2.4 ELECTRONIC MONITORING OF BEHAVIOUR

Electronic monitoring of adherence uses a device that looks similar to a standard medication container that has an electronic chip in the lid which records each time the patient opens the medication container; thus providing a computerised record of the time and date the bottle is opened. It is assumed that a dose is ingested each time the bottle is opened. These devises are usually referred to as medication events monitoring devices or microelectronic monitoring systems, both using the acronym MEMS.

MEMS is often referred to as the "gold standard" of adherence measurements (e.g. Arnsten et al., 2001, Osterberg and Blaschke, 2005, Partridge et al., 2002, Waterhouse et al., 1993, Cramer et al., 1990) and compared to other available measures of adherence it is generally considered to be the most valid and reliable method available to measure adherence. The MEMS also provide continuous scale out-put, as well as information about changes in adherence on specific days within the monitoring period. For example, both pill count and MEMS may show that the patient took 80% of doses. However, different to pill count, MEMS can show

exactly when these doses were missed during the monitored period. MEMS has been used in various studies on adherence to oral anticancer drugs (Lee et al., 1992, Waterhouse et al., 1993, Lee et al., 1993, Lee et al., 1996, Klein et al., 2006, Partridge et al., 2008, Marin et al., 2010). However, MEMS devices are expensive and are therefore primarily used in well funded clinical trials.

In addition, there are other limitations with using MEMS to assess adherence. For example, the patient may open the bottle without ingesting the medication, which would lead to overestimation of adherence, or may take out extra medication to store and subsequently ingest from another container, which would lead to underestimation of adherence (Bova et al., 2005, Wendel et al., 2001, Riekert and Rand, 2002, Bangsberg et al., 2000). Furthermore, patients who use monitored dosing boxes (e.g. Dosette) cannot use these adherence aids at the same time as using MEMS, but if these patients are excluded from adherence studies it could lead to selection bias (Wendel et al., 2001).

It is also possible that the use of MEMS will affect the patients' adherence. For example, if the patient is aware of the monitoring, the MEMS might work as an intervention that enhances adherence (Deschamps et al., 2006), although other studies found no such intervention effect on adherence from using MEMS (Wagner and Ghosh-Dastidar, 2002). On the other hand, the use of MEMS may increase unintentional nonadherence in patients who normally use monitored dosing boxes (Wendel et al., 2001).

Finally, in line with the other measurements already presented in this section MEMS monitoring unfortunately does not capture information about the patients' reasons for missing doses; this is where patients' self-report of adherence becomes so important.

1.8.2.5 SELF-REPORT

Self-report is one of the most widely used methods of measuring adherence to medication and is considered affordable, convenient, nonintrusive and easily administered. Self-report measures can be used prospectively or retrospectively and can be administered in a range of different settings, from face-to-face

interviews to large scale questionnaire surveys sent to patients' homes. Self-report can also be designed to produce either continuous scale data or categorical data, and as previously discussed continuous data is considered the superior output.

Prospective methods include the use of medication diaries. Patient using medication diaries are asked to record each time they are taking a dose. Prospective methods are less at risk for being biased by inaccurate recall by the patient. However, asking the patients to record their medication use every day may also feel intrusive and be cumbersome to keep up. It is very possible that the patient is not in fact recording each time a dose is taken, but rather fills in the diary for several days at a time at some later occasion (or just before an appointment). This means the diary may still be biased by the patient's incorrect recall, in addition to bias due to the patient not wanting to report actual nonadherence.

Retrospective self-report relies on the patient's accurate recall of how medication was taken. Self-report measures may ask whether the patient agrees or disagrees with a behavioural statement related to nonadherence; thus if the patient agrees that one or more statement applies to them they are classified as nonadherent, e.g. I sometimes forget to take my medicine (Morisky et al., 1986). Another method is to ask how many doses were missed during a specific time period or to estimate their adherence rate in percent on a visual analogue scale (Giordano et al., 2004). Nonadherence is thus often defined by a percentage cut-off point below which patients would be classified as nonadherent. Self-report has been used in several studies investigating nonadherence to oral anticancer treatments (Table 2, pp. 80)

Nevertheless, all self-report measures tend to overestimate adherence rates, in particular due to the patient not reporting actual nonadherence. This could be because of problems remembering instances of nonadherence or problems estimating own nonadherence rates. This bias can be minimised by asking for specific time periods, which are short and recent enough to increase the possibility of the patient remembering correctly. In addition, it is common that patients are reluctant to admit instances of nonadherence. This bias can also be reduced by asking the questions in a nonjudgmental manner and to frame the questions with statements that normalises nonadherent behaviour (Haynes et al., 2002). In

addition, a review analysing the concordance between self-report and non-self-report measurements found that self-reported adherence obtained by interviews had lower concordance with other measures than self-report obtained by questionnaires (Garber et al., 2004). This suggests that adherence assessed in interviews may generally have a lower validity than adherence assessed through using questionnaires.

A self-report approach to detect low levels of adherence with good sensitivity and specificity that has been recommended is to question whether the patient has missed one or more doses in the previous seven days. (Haynes et al., 2002, Hosek et al., 2005, Clifford et al., 2008). In this case nonadherence is defined as a patient reporting to have indeed missed a dose or more the previous week.

In addition to advantages of ease of administration and affordability, the greatest advantage with self-report measurements is that it is possible to capture underlying reasons for nonadherence and to differentiate between intentional and unintentional nonadherence. Intentional and unintentional nonadherence has different causes and would therefore require different focused interventions. None of the other measurement methods can capture patients' reasons for not adhering.

1.8.2.6 SUMMARY OF ADHERENCE MEASUREMENTS

It is evident that all adherence measurements have their advantages and limitations. Arguably no one measurement method can be recommended overall, rather it is important to tailor the adherence measurements according to the objectives of the assessment, such as clinical versus research purpose, illness group, the methods used and population under investigation (Chesney, 2006). For research purposes it is worthwhile to use multiple measures of nonadherence to reduce measurement error and to determine validity and reliability factors of the measurements, thus further enhancing our understanding of nonadherence (Chesney, 2006, Berg and Arnsten, 2006, Liu et al., 2001).

When funding allows, MEMS monitoring can be recommended as it is considered the most reliable and valid measure of adherence currently available. However, for larger scale epidemiology studies, medical records may be the only reasonable way

of measuring adherence. Where there are valid methods available to reliably measure biological or pharmacological markers of adherence these are very informative.

Finally, self-report is the only measure that can be used to capture patient reasons for not adhering as prescribed and is the only measure that can differentiate between intentional and unintentional nonadherence. Of the self-report measures retrospective methods are the least intrusive to the patient and generally the more convenient for research and practice purposes. Chapter 4 of this thesis is further expanding on the use of self-report measures by presenting the development and piloting phases of a novel self-report measure that aims to address some of the limitations of existing measurements.

1.9 RATIONALE FOR THE THESIS' FOCUS ON ADHERENCE TO ORAL ANTICANCER DRUGS

Cancer is the second most common cause of death in both males and females in the UK (National Statistics, 2006). In 2007, 298 000 new cases of cancer were diagnosed in the UK and the incidence rates for cancer in the UK increased by 25% between 1978 and 2007 (CRUK, 2010). However, during the same period cancer death rates fell by 20% (CRUK, 2010). The reduced mortality of cancer, which is most likely due to better cancer treatment and care, means that cancer is becoming more of a chronic disease.

Within secondary and tertiary cancer care in the UK, patients can be treated both as inpatients or outpatients. As inpatients the patients stay at the hospital during treatment, whereas outpatients stay at home during treatment but receive continuous care during outpatient clinics with their physician. The availability of self-administered oral anticancer drugs is steadily increasing, with several new agents having recently been introduced on the market in the UK, including oral capecitabine for colorectal cancer; imatinib and nilotinib for chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours; and oral topotecan for small-cell lung cancer (Aisner, 2007, Viele, 2007, NPSA, O'Neill and Twelves, 2002). This means patients are increasingly being treated as outpatients.

Cancer patients are generally viewed as being less at risk for nonadherence because of the acute seriousness of their illness. The lack of awareness of nonadherence to anticancer treatments may be related to the fact that cancer care has previously mainly been delivered in a hospital setting. In a hospital setting patients are closely monitored, thus minimising the risk of nonadherence. However, the increased use of oral anticancer drugs, which is often preferred by the patients (Liu et al., 1997, Borner et al., 2001), has led to a reduction in monitoring by the clinical team. As a consequence, nonadherence is likely to become more of an issue than it already is.

The consequences of nonadherence to anticancer drugs are serious. For example, nonadherence by taking less medication than prescribed can result in faster illness progression, avoidable morbidity and mortality, and increasing health care costs. Nonadherence due to over dosing, on the other hand, can lead to hospitalization and death (Birner et al., 2006, NPSA, 2008). In addition, nonadherence during clinical trials may lead to biased results and erroneous conclusions of drug effects.

The adherence literature is vast and there is an abundance of research into a range of chronic illnesses, such as asthma, diabetes, hypertension and HIV. In contrast there is very little research into adherence to oral anticancer treatments (Ruddy et al., 2009, DiMatteo et al., 2002). Table 2, on page 80, lists the published adherence studies that focus on adherence to oral anticancer drugs in adults. The studies were identified through two reviews (Partridge et al., 2002, Ruddy et al., 2009), and a hand search of all references retrieved. Three additional studies were identified. Two were specific to imatinib in CML and will be discussed in detail in the following section 1.9.1 (Darkow et al., 2007 and Noens et al., 2009). The third study was a longitudinal adherence study with breast cancer patients on Tamoxifen (Lash et al., 2006). The literature on adherence oral anticancer treatment is concentrated, thus studies and reviews cite each other comprehensively. Of the 18 studies presented in Table 2, only 11 were published before 2006 when the research for this thesis was initiated. In addition, of these 18 studies 9 focused on adherence to oral anticancer drugs for breast cancer.

As with other chronic illnesses, individual reports of adherence rates show broad variations. From Table 2 it can be seen that adherence rates to oral anticancer treatment of between 17%-100% have been reported, with variations most likely reflecting variations in patients' behaviour, as well as measurement methods and definitions used. Finally, nonadherence to maintenance therapy has been shown to increase with time in, for example, breast cancer (Chlebowski and Geller, 2006). In order to develop interventions to help cancer patients to adhere optimally to their treatment we need to improve our understanding of why cancer patients are nonadherent to their medication.

TABLE 2 SUMMARY TABLE OF ADHERENCE STUDIES WITH PATIENTS PRESCRIBED ORAL ANTICANCER TREATMENTS

Study	Cancer	N	Drug	Adherence/ persistence measure	Adherence/persistence rate	Time period
Levine Richardson Richardson 1987	Hematologic malignancy	108	Prednisone & allopurinol	Serum metabolites	Prednisone 26.8% Allopurinol 16.8%	6 months
Lebovits 1990	Breast cancer	51	Cyclophosphamide and/or prednisone	Self-report that 90-110% taken	53% overall with both drugs	6 months
Leventhal 1991	Ovarian cancer	11	Altretamine	MEMS	97% (SD=6.9%)	
Lee 1992	Lymphoma	21	Chlorambucil, prednisolone or dexamethasone	MEMS	100% (SD=20.6%)	852 days
Waterhouse 1993	Breast cancer	26	Tamoxifen	Self-report Pill count MEMS	97.9% (SD 3%) by self-report 92.1% (SD 9.8%) by pill count 85.4 (SD 17.2%) by MEMS	Mean no of months 2.92
Lee 1993	Small cell lung cancer	12	Etoposide	MEMS	93.2% (SD 12%)	298 days

Lee 1996	Ovarian cancer	11	Altretamine	MEMS	97.4% (SD 6.9%)	294 days
Sadahiro 2000	Colon cancer	57	Uracil-tegafur	Self-report Physician interview Urine level	94.4% at 3 mo, 94.7% at 1 yr by self-report and interview, 94.7% in range by urine testing of 38 patients at various time points	1 year
Murthy 2002	Breast cancer	53	Tamoxifen	Self-report	76% missed < 1 dose per week	6 months
Partridge 2003	Breast cancer	2 378	Tamoxifen	Prescription refill records	77% filled prescriptions that covered at least 80% of doses over the 1st year; 50% did so by 4th year	4 years
Grunfeld 2005	Breast cancer	110	Tamoxifen	Self-report	88% adherent	Not stated
Klein 2006	Myelodysplastic syndrome	90	Topotecan	MEMS	90%	5 – 10 days
Atkins 2006	Breast cancer	131	Tamoxifen	Self-report	55% reported nonadherence to medication frequently or occasionally	Single point in time
Lash 2006	Breast cancer	462	Tamoxifen	Self-report	31% had discontinued treatment at year 5	5 years
Barron 2007	Breast cancer	2 816	Tamoxifen	Prescription refill records	77.9% at 1 year 64.8% at 3.5 years	3.5 years
Darkow 2007	Chronic Myeloid Leukaemia (CML)	267	Imatinib	Electronic health claims data to calculate medication possession ratio (MPR= total days supply/365) & to	Mean MPR 77.7% and 31% of patients had treatment interruptions of 30 days or more	12 months

				identify treatment interruptions (failure to refill within 30 days from run-out date of prior prescription).		
Partridge 2008 – meeting abstract	Breast cancer	12 391	Anastrozole	Prescription refill records	78-86% of days were covered by filled prescriptions in Year 1; 62-79% of days were covered in Year 3	3 years
Noens 2009	CML	169	Imatinib	Pill count Self-report - visual analogue scale (VAS) Self-report of 'yes' or 'no' to 4 behavioural statements indicating nonadherence Spouse or family member VAS Physician VAS	At follow up: Mean pill-count 90.9 (SD 21.1; range 29-202%) Self-report VAS 95.7% (SD 6.1; N=169) Self-report 32.7% reported at least 1 of 4 behaviours indicating nonadherence. Spouse VAS 97.1 (SD 5.4; N=79) Physician VAS 94.9% (SD 9.9; N=167)	90 days

NOTE: This table is adapted and updated from Ruddy et al. 2009 and Partridge et al. 2002.

Initially I wanted to focus on a range of oral anticancer drugs. However, after consultation with a professor holding a senior position within Cancer Research UK and further reflection it was decided that I would focus my research on the oral anticancer drug imatinib (Gleevec® in US/Canada/Israel; Glivec® elsewhere; Novartis, Basel, Switzerland), which is the first line treatment for chronic myeloid leukaemia (CML).

There were two main reasons for choosing to focus on imatinib. Firstly, imatinib is a highly effective drug that in essence transformed CML from an often terminal illness; with the only long term cure previously involving risky bone marrow transplants, to a chronic illness that can be managed by the patient at home. However, this meant that the success of the treatment most likely would depend on the patients' ability to adhere as prescribed. Secondly, imatinib had at this point recently been licensed for use in the UK in 2003 and no studies had yet been published that investigated patients' adherence to this drug.

The School of Pharmacy already had established research links with Imperial College London NHS health care trust and Hammersmith Hospital, which is one of the centres of excellence for treating CML in the UK. Contact was therefore made to propose the possibility of conducting an exploratory study of CML patients' medication taking behaviours in terms of imatinib. It was revealed that a purely quantitative clinical trial investigating associations of imatinib adherence and clinical response in CML patients had just started to enrol patients.

A meeting with the clinical trial lead was set up and our common aims in understanding adherence in this patient group became immediately apparent. The interview study was the perfect complement to the clinical trial as the combination meant we would investigate the extent and impact of nonadherence in this group, as well as the patients' reasons why doses were missed or not. The insights shared in the partnership during the clinical trial and interview studies, with me and my supervisors coming from a health psychology / pharmacy understanding of patient behaviour and the clinical trials team coming from a biomedical understanding of

illness and treatment, gave many valuable insights during the analysis and interpretation of both studies.

1.9.1 ADHERENCE TO IMATINIB IN PATIENTS WITH CHRONIC MYELOID LEUKAEMIA

This section will give a brief background on chronic myeloid leukaemia and the imatinib treatment. In addition, the studies that have now been published on adherence to imatinib will be introduced.

Chronic myeloid leukaemia (CML) accounts for approximately 15% of all leukaemias (blood cancers) in adults, which in turn constitute about 2% of the yearly cancer incidence in the UK (CRUK, 2010). In the UK it is estimated that 560 people are diagnosed with CML each year, which is slightly more common in men than women with a ratio of men:women being 1.2:0.7 per 100,000 (NICE, 2010). The median age at diagnosis is 60 years (NICE, 2010).

CML is a cancer of the blood in which the bone marrow produces too many, and often dysfunctional, white blood cells. CML has three phases. The initial chronic phase lasts between 3 and 5 years and 90% of patients are diagnosed during this phase. In approximately 40% of these patients CML is asymptomatic and is diagnosed as a result of a routine blood test. If left untreated the CML then progresses to the accelerated phase, which lasts for about 6 months. During this phase the disease progression is more rapid and immature cells proliferate in the blood and bone marrow. At this phase the symptoms include bruising, bleeding and infections. The final phase of the CML is called a blast cell crisis. This phase is characterised by a rapid increase in immature cells that replace the normal blood cells in the bone marrow and affect other organs. When this phase is reached CML is usually fatal within 3–6 months (NICE, 2010).

CML is characterized by a consistent chromosomal abnormality, which carries a unique fusion gene, termed BCR-ABL1 (Goldman and Melo). The BCR-ABL1 fusion gene comprising of the ABL gene from chromosome 9, which have broken off and

fused with the BCR gene from chromosome 22, creating the 'Philadelphia Chromosome' (Ph+) found in 95% of all CML patients. The BCR-ABL1 fusion gene produces a tyrosine kinase protein transcript that continuously activates and speeds up the production of white blood cells. The result is a build-up of white blood cells, and a reduction of other vital blood cells such as the red blood cells that carries oxygen around the body, and platelets which allow for the blood to coagulate. In the absence of treatment, CML is inexorably fatal. Nonetheless, CML is unique amongst cancers in that a specific chromosomal abnormality has been identified as the cause of the illness, which has allowed for the development of highly effective drugs that target this abnormality (Druker, 2008).

In 1990 imatinib revolutionised the treatment of CML and after successful clinical trials was licensed in the US as first line treatment in 2001, with the United Kingdom following suit in 2003. Imatinib selectively inhibits the enhanced tyrosine kinase activity of the protein encoded by the BCR-ABL1 fusion gene and induces durable cytogenetic responses in the majority of patients with relatively few side effects (Goldman and Melo). In approximately 75% of patients the Ph^+ chromosome is no longer detectable after two years of therapy (a status referred to as complete cytogenetic response or CCyR)(Druker et al., 2006, de Lavallade et al., 2008). The achievement of CCyR is the major objective of therapy since it is associated with prolonged survival (Druker et al., 2006, de Lavallade et al., 2008, Bonifazi et al., 2001).

In patients who achieve CCyR, BCR-ABL1 transcript levels may be monitored using real-time quantitative polymerase chain reaction (PCR) to assess the quantity of residual leukaemia. It is generally accepted that CCyR corresponds to an approximately 2-log reduction (a reduction by 99%) in transcript levels (Lin et al.). By 5 years approximately 50% of CML patients taking imatinib will have achieved a 3-log reduction (a reduction by 99.9%) in transcript levels (defined as a major molecular response or MMR) (de Lavallade et al., 2008); this confers further clinical benefit (Marin et al.) and it is also considered an important therapeutic target (Baccarani et al., 2006). The five-year progression-free survival of CML

patients who has achieved MMR on imatinib is 99%; and perhaps more importantly, the risk of progression for these patients became less each successive year from diagnosis to reach zero after year 3 (Apperley, 2007b).

With continued treatment about 20-30% of patients eventually achieve a 4-log reduction (a reduction by 99.99%) and in at least 10% of patients the transcripts will become undetectable (complete molecular response or CMR)(de Lavallade et al., 2008). In some cases durable CMR may be the equivalent of "cure" as it is possible to discontinue treatment in some of these patients without subsequent relapse (Rousselot et al., 2007, Mahon et al., 2002). Nevertheless, the continuous management of the chronic leukaemia now depends on patients' ability and motivation to adhere to imatinib as prescribed.

Since the research presented in this thesis was initiated in 2006, two studies have been published, which suggest that nonadherence may be frequent in CML patients taking imatinib and that the consequences are severe (Darkow et al., Noens et al.)

The ADAGIO study conducted in Belgium, found that one third of the 169 patients included in their sample were nonadherent, and only 14.2% were perfectly adherent at 100% imatinib taken (Noens et al., 2009). Nonadherence according to pill-count was found to be associated with reduced clinical response in this patient group. A range of patient related factors were associated with higher nonadherence, for example, higher age, longer time since diagnosis, living alone and male sex (Noens et al., 2009).

In addition to reduced clinical response, nonadherence to imatinib in CML patients has been shown to increase health care costs (Darkow et al., 2007). This US study, investigated whether imatinib nonadherence was associated with patient characteristics and healthcare costs. The study used medication possession ratio (MPR) as a proxy measure of adherence. The MPR was calculated using retrospective electronic health claims data for 267 CML patients. The total days' supply of all imatinib fills was divided by the 365 days follow-up period (any over supply was truncated at 100%). The results revealed a mean MPR of 77.7% (SD

27.5%). Forty-six percent of patients had an MPR <90%, 20% of patients had an MPR <50% and 30.7% of patients were identified as having treatment interruptions of at least 30 consecutive days during the follow-up period. The results indicated that women have significantly lower MPR, and were more likely than men to have treatment interruptions. In addition, increased pill-burden (number of different drugs prescribed for each patient) and being initiated on 600mg imatinib was associated with decreased MPR. The results further showed that reduced MPR was related to increased healthcare and medical costs in this patient group (Darkow et al., 2007).

In addition, our article from the UK clinical trial that the interviews presented in this thesis are related to was published earlier this year. The results suggested that nonadherence may be the predominant reason for poor clinical response in CML patients (Marin et al., 2010). This paper will be discussed further in the introduction of Chapter 2.

What these studies do not tell us, however, is why CML patients are nonadherent. Understanding the patients' reasons for why they are not taking their medication as prescribed is the first step towards developing appropriate theory to explain the behaviour and work towards solutions. This thesis will therefore provide the exploratory groundwork that will increase our understanding of the medication taking behaviour of patients prescribed oral anticancer drugs, using CML patients on imatinib as the paradigm of investigation. The following section will set out the specific aims and objectives of this thesis.

1.10 AIMS AND OBJECTIVES OF THESIS

The aim of this thesis is to understand cancer patients' reasons for taking or not taking oral anticancer drugs as prescribed, as well as to develop theory and measurements related to nonadherence. To reach this aim, the thesis used the adherence related behaviour of chronic myeloid leukaemia (CML) patients prescribed the oral anticancer drug imatinib as the paradigm of investigation and the following objectives were set up.

1) To understand CML patients' reasons for nonadherent behaviour in relation to the oral anticancer drug imatinib.
    a. To explore factors associated with intentional nonadherence to imatinib.
    b. To explore factors associated with unintentional nonadherence to imatinib.
    c. To explore factors associated with achieved adherence to imatinib.
    d. To explore patterns of nonadherence.
2) To explore the usefulness of Reason's Accident Causation Framework (ACF) (Reason, 1990) in explaining patients' reasons for nonadherence to prescribed medication.
    a. To explore the applicability of the ACF to explain nonadherence to imatinib in CML patients.
    b. To develop the ACF to better explain nonadherence to medication.
    c. To adapt terminology and definitions to be better suited to the field of medication adherence.
3) To develop and pilot an adherence scale grounded in theory.
    a. To develop an adherence scale to measure a single medicine.
        i. To pilot validity of the adherence scale for a single medicine.

b. To develop an adherence scale to measure adherence to multiple medicines.

As an overview of the coming chapters, chapter 2 will present a study using in-depth interviews to explore CML patients' experiences and behaviour related to using the oral anticancer drug imatinib. Chapter 3 examines the usefulness of the ACF in explaining nonadherence to oral anticancer drugs through a post-hoc analysis of the interview data from the chapter 2 study. Chapter 4 presents the development and pilot evaluations of two versions of a novel adherence measurement scale. Chapter 5 will conclude by discussing the novel contributions of this thesis to knowledge and critical thinking to the field of medication adherence, as well as discussing limitations and implication for future research and practice.

Chapter 2: Exploring chronic myeloid leukaemia patients' reasons for Imatinib taking behaviour

2.1 INTRODUCTION

Nonadherence seems to be frequent in chronic myeloid leukaemia (CML) patients prescribed imatinib. To intervene and support patients to achieve optimal adherence we need to understand the reasons why many CML patients do not adhere to their oral anticancer drugs as prescribed. However, no previous research has explored CML patients' reasons for not adhering to imatinib, which is the aim of the current study. Table 3 contains information about the medication imatinib.

TABLE 3. KEY INFORMATION REGARDING IMATINIB AS INDICATED FOR CHRONIC MYELOID LEUKAEMIA IN THE UK

Imatinib (Glivec/Gleevec) is a tyrosine kinase inhibitor recommended as first line treatment for chronic phase CML (British National Formulary 60, 2010). In the UK imatinib is available as 400mg and 100mg yellow-brown tablets and can be dispersed in water or apple juice if needed. The dose for adults is 400mg once daily, which can be increased if necessary to a maximum of 800mg twice daily. Imatinib is also indicated for the accelerated and the blast crisis phases of CML on a dose of 600mg once daily to be increased if necessary to a maximum of 800mg twice daily. There are interactions reported with several commonly prescribed drugs, e.g. simvastatin and warfarin, as well as with the natural remedy St John's Worth. Imatinib should not be used during pregnancy and effective contraception is required during treatment (British National Formulary 60, 2010). Common side effects include nausea, asthenia, fatigue, anaemia, oedema, gastro-intestinal problems and muscle cramps, as well as bone and joint pains (British National Formulary 60, 2010). Despite these side-effects, however, imatinib is generally considered to be well tolerated (Moen et al., 2007).

Noens et al. (2009) found that one third of the 169 patients included in their sample were nonadherent, and only 14.2% were perfectly adherent at 100%

imatinib taken. Nonadherence according to pill-count was found to be associated with reduced clinical response in this patient group. In addition to reduced clinical response, nonadherence to imatinib in CML patients has been shown to increase health care costs (Darkow et al., 2007).

The patient sample that is used as the paradigm of investigation of this thesis were already enrolled in a NIHR funded UK clinical trial that investigated the relationship between imatinib adherence and clinical response. Briefly, eighty-seven patients with chronic phase CML participated in the clinical trial (Marin et al., 2010). The patients had been treated with imatinib 400 mg/day for a median 60 months (min-max 25-104). Adherence was monitored for 3 months using Medication Event Monitoring Systems (MEMS; Aardex©, Zug, Switzerland). MEMS is an electronic device fitted in the cap of a medication bottle of standard appearance that records the time and date on each occasion the bottle is opened (Figure 7, pp. 93). Patients were not told there was an electronic chip in the MEMS that would monitor them, although they were told their adherence would be monitored using pill-count. This approach was reviewed and approved by an NHS ethics committee. At baseline and follow-up, patients described their side-effects and completed a quality of life questionnaire (FACT-G).

Median adherence-rate was 98% (min-max 24-104%). Although, twenty-three patients (26%) had adherence ≤90%, and of these 12 patients (14%) took 80% or less. The younger patients were more likely to have a lower adherence rate to therapy. The median age for patients with an adherence rate ≤90% was 43.8 years, versus 53.8 years for patients with a rate >90% (p=0.004). Furthermore, a significantly lower adherence rate was found in patients suffering asthenia, nausea, muscle cramps and bone or joint pains. Adherence and overall quality of life as measured with the FACT-G questionnaire were unrelated. However, patients who scored in the lowest quartile of the physical well-being subscale of the FACT-G had a lower adherence rate than the others (88% vs 95% respectively, p=0.05). The trial results revealed that poor adherence may be the predominant reason for

failure to obtain adequate clinical responses in CML patients who have been treated with imatinib for 2 years or more (Marin et al., 2010).

The above studies show that nonadherence to imatinib is common in CML patient groups and that it has significant adverse effect on health. This is unfortunate as achieving a complete molecular response, where no residual leukaemia can be detected in the body, could constitute a "cure". When this has happened patients have been able to discontinue treatment without subsequent relapse (Rousselot et al., 2007, Mahon et al., 2002). Even though these three studies have given some indication of factors associated with poor adherence, these factors are somewhat contradictory between the studies. For example, Noens et al. (2009) found that males were more likely to be nonadherent, Darkow et al. (2007) found that females were more likely to be nonadherent, whilst Marin found no association with sex and adherence; Noens et al. (2009) found that older patient were more likely to be nonadherent, whilst Marin et al. (2010) found that younger patients were more likely to be nonadherent; and Noens found no association with side effects and nonadherence, whilst Marin et al. did find such associations etc. These inconsistencies highlight the difficulty in finding consistent predictors of nonadherence and illustrate the need for further research into exploring why CML patients are nonadherent to oral therapy.

FIGURE 7 MEDICATION EVENTS MONITORING SYSTEM (MEMS; AARDEX ©, ZUG, SWITZERLAND). THE MEMS DEVICE REPLACES THE LID OF THE MEDICATION BOTTLE

Understanding the reasons why patients are nonadherent is essential to develop interventions to help patients to better adhere to their oral treatments, but to date nobody has investigated the reasons why CML patients are nonadherent to imatinib therapy. There is also a distinct lack of qualitative studies exploring cancer patients' experiences with taking oral drugs in general. A review synthesising qualitative studies that explored patient experiences with taking medicine included only one study with cancer patients, which focused on medicine to control pain rather than anticancer drugs to treat the cancer per se (Pound et al., 2005, Ersek et al., 1999).

Nonetheless, these syntheses gave insight into the patients' perspective of treatment regimens and related medication taking behaviours. These reviews concluded that patients are mainly resisting taking medicines because of concerns about the medicines themselves, rather than failures in professionals, patients and systems (Pound et al., 2005, Nunes et al., 2009). The syntheses found that patients use a range of ways to evaluate their medicines, including considering the extent of adverse effects experienced; stopping the treatment for a period to see what

happens; considering clinical feedback of treatment response and subjective experience of illness symptoms; and weighing the clinical benefits of controlling the illness against adverse effects and disruption to daily routines (Pound et al., 2005, Nunes et al., 2009). However, at times it was difficult for patients to distinguish between illness symptoms and adverse effects of the treatment.

Consequently, based on the patients' lay evaluations, a range of different ways in which patients take their medicines became apparent across the different studies included in the syntheses (Pound et al., 2005, Nunes et al., 2009). Patients were often found to try and minimise intake of medicines, in particular to decrease adverse effects. In addition, patients may modify their regimen to better fit it with their daily life. In these cases patients would at times express an opinion that full adherence is not necessary to get the clinical benefit of the treatment and that perfect adherence is in practice unachievable. Patients may also adjust doses as they see fit and may not take the medication if drinking alcohol of fear of possible interaction. It was also reported by the authors of the syntheses (Pound et al., 2005, Nunes et al., 2009) that patients would rarely tell their doctors if they had been missing doses.

Qualitative studies are generally less driven by existing theories than quantitative research and are instead concerned with building an understanding of a phenomena by using words instead of numbers (Miles and Huberman, 1994). Only after this is done, explanatory theory is captured as it emerges from the data, or the researcher evaluates the ability of existing theories to explain the findings. The tendency for psychology as a discipline to apply empirical methods to explain complex behaviour has been criticised (Murray and Chamberlain, 1999) and there has been a move towards an increased appreciation and implementation of qualitative methods (Miles and Huberman, 1994). Qualitative research is particularly important when entering a new area of investigation, where little pre-existing understanding is available, to lay the groundwork and direct future research. In terms of adherence to oral anticancer medication, health care providers and researchers may harbour assumptions and preconceived ideas

about patients' experiences that are simplified or untrue, which could lead to the use of theory or the development of interventions to address the problems that are inappropriate. Instead, theory and interventions should incorporate the patients' perspective on the reasons for why they sometimes miss doses and how others achieve adherence. This can only be achieved by allowing the patients' voice to be heard.

This chapter reports a qualitative study that explored CML patients' reasons for taking, or not taking, their imatinib as prescribed. Intentional and unintentional nonadherence have different causes and thus require different solutions (WHO, 2003, Nunes et al., 2009), these interviews are therefore focusing specifically on both intentional and unintentional factors affecting instances of nonadherence.

2.2 AIMS AND OBJECTIVES

The aim of this study was to better understand CML patients' reasons for taking, or not taking, imatinib as prescribed. To reach this aim the following objectives were set up.

1) To explore factors associated with intentional nonadherence to imatinib.
2) To explore factors associated with unintentional nonadherence to imatinib.
3) To explore factors associated with achieved adherence to imatinib.
4) To explore patterns of nonadherence.

2.3 METHODS

2.3.1 RATIONALE

There have been no previous studies exploring the issues facing chronic myeloid leukaemia (CML) patients who are prescribed imatinib and there is no literature on why many of these patients are not taking their imatinib as prescribed or how other CML patients do achieve adherence. Qualitative research methods are used

to explore these types of questions of why a phenomenon appears, as well as explore in-depth how phenomenon develops, changes and interact with other variables within a local context (Miles and Huberman, 1994). In addition, qualitative methods are often used to develop theory and hypothesises, which can in turn drive further research in that particular area.

To explore CML patients' experiences with using imatinib it would have been possible to use either focus groups or in-depth interviews. In-depth interviews were deemed to most appropriate as intimate details of the patients' illness and treatment experiences were to be explored, which the patients may not want to discuss openly.

In terms of the qualitative analysis that was chosen, it was initially planned to perform a theory driven framework analysis (Ritchie and Spencer, 1994, Ritchie et al., 2003) as one of the aims of this thesis was to explore the usefulness of Reason's Accident Causation Framework (ACF) (1990) in explaining nonadherence to oral anticancer medicines. However, upon reflection it was decided the first 4 interviews should be analysed using the constant comparison aspect of a general grounded theory approach (Glaser and Strauss, 1967, Strauss and Corbin, 1998, Chamberlain, 1999) in order for the coding framework to emerge from the data, rather than directly force a theory onto the data set. After these first 4 interviews had been analysed, however, it felt too early to combine the emerging coding framework with the ACF. It was therefore decided to continue the constant comparison analysis to conduct and analyse all the patient interviews (which are presented in this chapter) and instead perform a post-hoc analysis of the complete data set using a framework analysis driven by the ACF (which is presented in chapter 3). This was meant to reduce the risk of missing out on important insights about the patient experiences with taking, or not taking, imatinib as prescribed.

2.3.2 STUDY DESIGN

Qualitative research is based on patients' narratives about their experiences and thoughts. The data is highly interpretative and there are challenges with assuring that qualitative research is robust. Robust research refers to research that is valid and reliable; validity of the data refers to the data being interpreted correctly as what it actually is, whilst reliability refers to the data interpretation being reproducible and consistent (Bowling, 2001). Miles and Huberman (1994) argue that the issue of validity and reliability in qualitative research lies primarily with the skills of the researcher.

However, certain measures can be taken to ensure that qualitative data collection and interpretation has a good chance of being valid and reliable. It is important to acknowledge the biases that may arise because of the researcher's preconceptions about the study area. It has been argued that researcher bias may be particularly salient in qualitative research as it is common that the researcher both develop the means by which to collect the data, collect data and perform the analysis (Bowling, 2001, Miles and Huberman, 1994). Therefore, one method used to minimise researcher bias is triangulation (Kimchi et al., 1991). There are several different ways of using triangulation via data collection, analysis of data or investigators. The current investigation used investigator triangulation to ensure robustness of the study, which refers to using more than one researcher to explore the same phenomena. In line with this, a proportion of the data collected in the project was coded by two different researchers, and ongoing discussion of emerging themes and codes was held between the research group (LE, SC and NB). In addition, the data was presented in a transparent and accessible manner so that arguments and interpretations can be followed by anyone interested (Miles and Huberman, 1994). How validity of this study was addressed will be discussed further in section 2.3.5.

2.3.3 PARTICIPANTS AND CONSENT

The qualitative study was approved by Lewisham NHS medical research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

On completion of the clinical trial (ClinicalTrials.gov identifier: NCT00632255; discussed in detail in the introduction section 2.1), investigating the effect of adherence on clinical response (Marin et al., 2010) all participants were sent an invitation letter, the information leaflet and the consent form (Appendix A) about participating in an interview regarding their experience with taking imatinib by a clinical trial nurse. After the clinical trial nurse had received an initial verbal or written (email) consent that the patient was happy to be interviewed, the principal investigator (LE) contacted the patient by phone to arrange a convenient time to conduct the interview.

The patients could choose to be interviewed in a quiet room in the hospital or in their own home, whichever they preferred. After initial verbal consent was taken by the trial nurse, written informed consent was taken by the interviewer at the start of the interview. Participants were reassured of the confidentiality of personal information and the strict anonymity of all information that would be reported. In order to protect the interviewees' identities, information that could be used as an indirect identifier in the extracts reported in this chapter, such as occupation, sex and geographic places, have been altered or are not reported at all.

This is qualitative research which does not quantitatively test a hypothesis nor estimate incidence or prevalence. Therefore, sample size was not determined based on statistical power. Instead, theoretical sampling was ongoing during the study and I aimed to sample all patients who were identified as nonadherent according to the clinical trial MEMS reading (adherence rate ≤90%). In addition, in order to hear narratives about adherent behaviours the patients were sampled on a one to four ratio, with one adherent patient (MEMS adherence rate >90%)

recruited for every four nonadherent patients that were recruited. The sample size in terms of adherent patients was ultimately determined by the point at which the data had reached 'theoretical saturation', that is the point were no significant new information regarding adherence or nonadherence (many adherent patients also had experienced instances of nonadherence) emerged from the data (Glaser and Strauss, 1967).

2.3.4 DEFINITION OF ADHERENCE

To identify participants for the interview study, adherent and nonadherent patients were dichotomised in accordance with the 3 months adherence MEMS data emanating from the clinical trial (Marin et al., 2010). The results from the clinical trial indicated 90% was the adherence level below which nonadherence had a significant adverse effect on clinical response. Therefore, 90% was used as a cut off point to dichotomise adherent and nonadherent patients.

Each interview was initiated with a relaxed chat about the patient's everyday life such as hobbies, holidays, or whatever topic came up. In most interviews it was a natural move towards talking about the CML and the treatment and at this point, in order to pick up on indications that patients might have problems adhering to their imatinib, they were asked two questions 1) "It is common that patients at times miss a few doses, for a whole range of reasons, thinking of the past 7 days have you missed any doses?"; and 2) "It is also common that patients at times change their dose, for a range of different reasons, thinking of the past 7 days have you changed the dose and taken more or less than the doctors say?". This approach has been recommended as it has good sensitivity and specificity to detect low levels of adherence (Haynes et al., 2002). If a patient answered yes to either of these questions it was taken as an indication that the patient had problems with adherence.

Intentional nonadherence was defined as the patient deciding to alter or discontinue their treatment. Unintentional nonadherence was defined as the patients intending to take their medication as prescribed, but is unable to do so.

2.3.5 DATA COLLECTION AND ANALYSIS

The interviews were conducted and analysed in accordance with the constant comparison aspect of a general grounded theory approach (Glaser and Strauss, 1967, Chamberlain, 1999). The interviews were semi-structured and followed a topic guide (Appendix B). In accordance with the constant comparison aspect of grounded theory the topic guide was continuously updated as new topics emerged (Appendix C). This approach to interviewing required ongoing data analysis during the whole interview period.

The interviews were digitally recorded, transcribed verbatim and analysed using the software MAXQDA 2007. The transcripts were coded and emerging themes were constantly compared to and included into the coding framework, thus thematically describing the data (Glaser and Strauss, 1967). All the coded segments were charted in a spreadsheet to give clear overview of the analysis and to make the data accessible, transparent and easy to understand for everyone in the research team (Miles and Huberman, 1994)

After the interview the trial nurse filled in the patient information sheet (Appendix D), which included information about the time of diagnosis, treatment regimen, response to treatment and adherence classification according to the 3 months MEMS data from the clinical trial.

All transcripts were read and coded by the chief investigator (LE). To ensure validity and reliability the first 5 transcripts were separately coded by a second researcher (SC). The coding frameworks were compared and thoroughly discussed after the coding of each of these 5 transcripts was completed. Subsequent coding was carried out by the chief investigator, but regular meetings were held by the research group (LE, SC and NB) to discuss themes emerging from the data. Finally,

a random sample of 3 other transcripts of nonadherent patients was double-coded by SC to ensure reliability in the use of the coding frameworks.

2.3.6 PATTERNS OF NONADHERENCE

To explore patterns of nonadherence of the patients who participated in the interviews the MEMS results for these patients were collected and screen shots were taken of the calendar plots and the chronology charts. The calendar plots (Figure 8) display the MEMS results as a calendar. Green coloured days indicate that the MEMS has been opened the correct number times, depending on the prescribed number of doses. Two openings can either refer to two openings by the same MEMS monitor or one opening each of two different MEMS monitors. In this sample, 11 patients used a single MEMS monitor and 10 patients used two MEMS monitors. The reasons for this was that either the patients had been prescribed 500mg or 600mg imatinib, which would have been dispensed as 400mg and 100mg tablets, or the patient simply had too many doses to fit into one MEMS monitor. Yellow coloured days indicate days the incorrect number of openings have been performed, either too few or too many; zero openings are marked with a red zero.

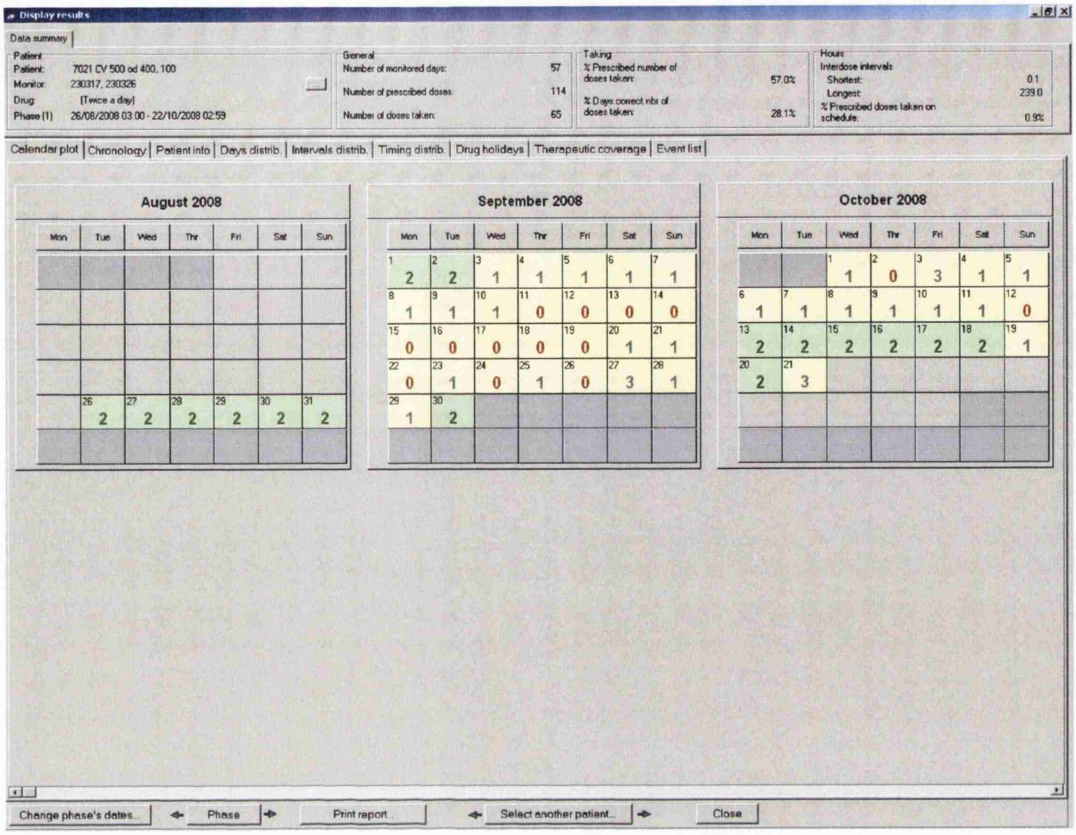

FIGURE 8 MEMS DATA DISPLAYED AS CALENDAR PLOT, PATIENT 13

The MEMS chronology (Figure 9) displays the data by charting the bottle openings over the time of the day (Y axis) and over days of the month (X axis). In this display:

- Blue dot indicate first monitor was opened
- Orange triangle pointing upwards indicates second monitor was opened
- Red triangle pointing downwards indicates 1 of 2 monitors was not opened
- Red vertical line indicate all doses were missed that day
- Blue cross indicate that opening has been excluded by the person who collected the MEMS data (exclusions could have been done for a range of different reasons, including openings done by the patient or a health care professional during a hospital appointment without the patient having ingested imatinib tablets)

- Grey boxes at the bottom of the display indicate weekend days (Saturday and Sunday)

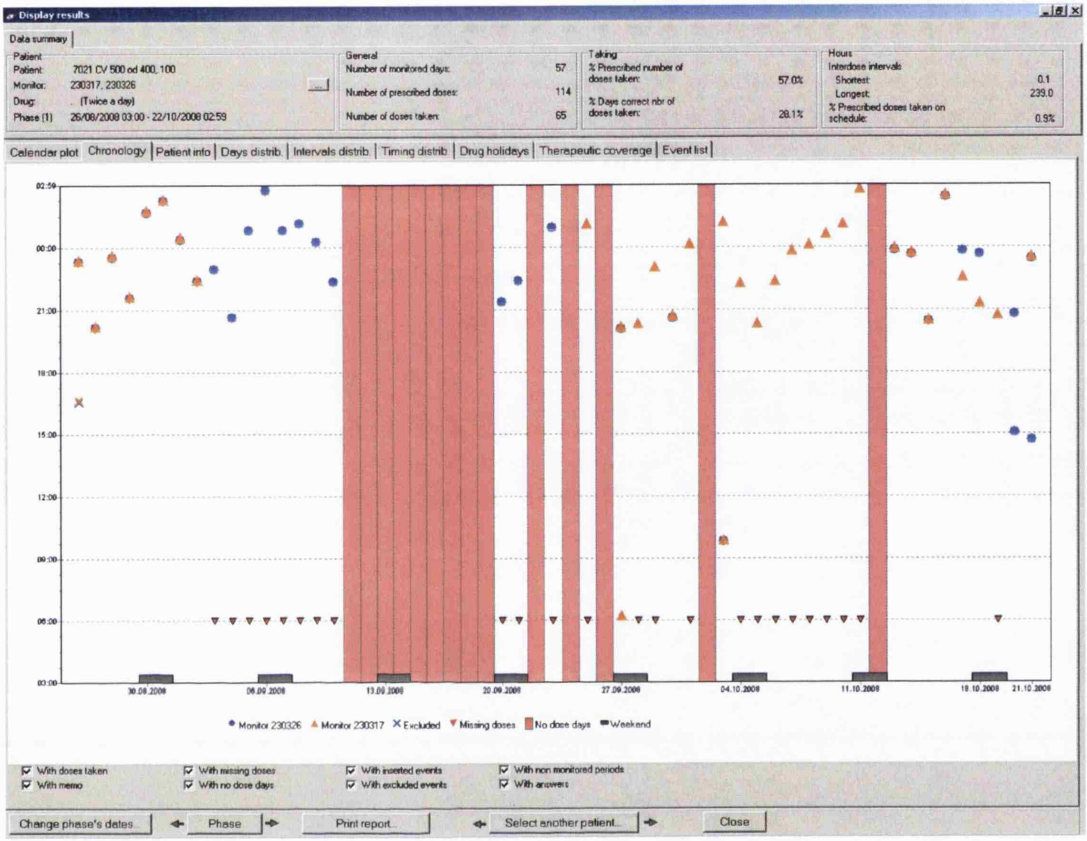

FIGURE 9 CHRONOLOGY DISPLAY OF MEMS DATA, PATIENT 13

During the whole period when interviews were conducted the interviewer did not have access to any of the MEMS data. These were collected after the interviews had already been analysed and written up. The analysis included first making a short summary of the patients' narratives relating to adherence/nonadherence. In addition, short qualitative summaries of the calendar plots and the chronology charts were done for each patient. Subsequently, the summaries of the patients' narratives and the patient MEMS readings were then analysed for specific patterns of adherence/nonadherence. Finally, the MEMS chronology plots were charted according to the specific patterns of adherence/nonadherence that could be identified.

2.3.7 PATIENT FEEDBACK SESSION OF STUDY RESULTS

A feedback session was organised after all data analysis had been completed in April 2010. The aim of the feedback session was to disseminate the results of the clinical trial and the interviews to the patients, discuss the methods that had been used in the clinical trial, as well as collect patient feedback.

The afternoon session consisted of a three part presentation of about 15 min each, followed by a reception. The first part presented the methods used in the clinical trial, with particular focus on telling the patients that medication events monitoring systems (MEMS) had been used to monitor their adherence rates without their knowledge. The revelation of the MEMS method was framed by explaining the difficulty in measuring behaviour (i.e. adherence to medication) without influencing it and the importance of minimising result bias in obtaining valid trial results. The ethics approval procedures were briefly explained and ethical implications of withholding information was discussed. It was also explained that had anyone asked specific questions about the way we would monitor adherence rates they would have been told of the MEMS. The second part presented the results of the trial and the focus was on the importance of adherence in achieving a good response to imatinib. It was explained, however, that patients are doing well even if they are not reaching a complete molecular response. The third part presented presenting the results of the interviews, discussing reasons why many patients missed doses of imatinib and why other patients did not miss doses.

We used a brief feedback form (Appendix E) to collect feedback on whether the attendants (including patients, partners/family/friends of patients and staff of Hammersmith Hospital) found the session useful, as well as their opinions regarding the use of MEMS and the results from the interviews. Frequencies and graphs were processed using Predictive Analytics Software (PASW) statistics 18.

2.4 RESULTS

Eighty-seven patients participated in the clinical trial (Marin et al., 2010), of which 23 (26%) were nonadherent and 64 (74%) were considered adherent according to 3 months MEMS readings at 90% cut-off for doses taken. Patients had been monitored by MEMS for a median of 83 days (min-max = 40-120; IQR=7). The patients were not told before starting the trial that their adherence would be monitored using the MEMS device. However, the patients had been told that their adherence would be monitored using pill-count.

Of the 23 nonadherent patients 17 were interviewed. Of the remaining 6 nonadherent patients, one patient agreed to be interviewed but it was then not possible to get hold of the patient to book an appointment, the other five patients did not respond to the invitation letters and did not answer reminder phone calls made by the trial nurse.

Of the 64 adherent patients 30 agreed to be interviewed and 34 did not respond. However, the adherent patients were not contacted through reminder phone calls as only 4 adherent patients were interviewed. It is possible more adherent patients would have agreed to be interviewed had they been reminded. In total 21 adherent and nonadherent patients were interviewed between November 2008 and July 2009.

2.4.1 THE INTERVIEW PROCESS AND PATIENT CHARACTERISTICS

The patients could chose if they wanted to be interviewed at home or in a quiet room at the hospital. Six patients chose to be interviewed at home and the rest were interviewed at the hospital before or after their routine clinical appointment. The patients seemed to mainly make this choice based on convenience of being interviewed when they were at the hospital for an appointment or at home if they did not have an appointment scheduled in the near future.

The six patients interviewed at home were all welcoming; always offering a cup of tea and being open and friendly. In all instances except one the patient was the only adult present during the interview. In two cases children were present but never disruptive and in one case the patient's wife was present for about 10 minutes of the interview.

All the interviews varied in time from about 30 minutes to two hours. The inter views at the hospital tended to be around 1 hour, whilst interviews conducted at patients' home often lasted a bit more than one hour. In one case I stayed at a patient's home for about 3 hours; although by 2 hours I switched off the recorder and spent the last hour looking at photographs and chatting generally about life, gardening and grandchildren.

The patients had varied occupational backgrounds spanning the police, banking, accountancy, IT and insurance, as well as a university student and six pensioners. There were some patients who had changed work/work responsibilities, reduced their work load, taken early retirement or were on long term sick leave because of the CML. There was no one who stated they were unemployed. There were also two women who were stay at home mothers; one who was not looking for a job and one who had recently started to apply for jobs.

Eleven patients were married/lived with partner and had children (some with young children and some with older children who did not live at home), two patients were older widows with grown up children, one patient had a child but lived separately from the child's father, one patient had grown up children and were either widowed or divorced since a long time, three patients were married with no children and three patients were single with no children.

2.4.2 INTERVIEW RESULTS

As can be seen in Table 4 on the following page, 17 of the 21 interviewees were classified as nonadherent according to the 3 months MEMS data, with an adherence rate ≤90. Eight of the 17 patients who according to MEMS were

nonadherent also stated in the interview to have missed one or more doses in the last 7 days. There was a time gap between the end of trial and the interviews of several months in most cases, therefore the fact that patients who were found to be nonadherent during the trial did not report nonadherence in the last 7 days may only be a reflection of this time difference. Furthermore, the MEMS readings were over a longer time period, which may also influence the recorded adherence rate. However, four patient who had MEMS adherence ≤90% stated they had never missed a dose. This could be due to the patient not wanting to report nonadherence or could be due to incorrect MEMS reading, which will be discussed further in section 2.4.3.8 (pp. 125) on the influence of trial procedures on recorded adherence rates.

Four of the 21 interviewees were adherent according to MEMS with an adherence rate >90% (Table 4). All 4 patients who were classified as adherent according to MEMS also stated they had not missed any doses in the past 7 days.

TABLE 4 PATIENT DETAILS OF THE INTERVIEW SAMPLE

MEMS classification	N	Age median years (min-max; IQR)	Sex (males/females)	MEMS adherence rate	Missed dose in last 7 (yes / no)
Nonadherent	17	41 (26-70; 25)	11 males/6 females	≤90%	8 yes / 9 no
Adherent	4	57 (33-70; 31)	3 males/1 female	>90%	0 yes / 4 no
Total	21	50 (26-70; 26)	14 males/7 females		8 yes / 13 no

The results of the analysis of the interview exploring CML patients' experiences with using imatinib, including meta-categories, themes and sub-themes are shown in Table 5. The meta-categories were adherence, nonadherence and medication

management. The following exploration of nonadherence and adherence to imatinib therapy will first present the findings from the interviews. Thereafter, the different patterns of nonadherence that were displayed in this sample will be presented. Finally, the results and the reflections from the patient feedback session will be presented, before moving on to the general discussion of this chapter.

TABLE 5 RESULTS FROM THE INTERVIEWS: META-CATEGORIES, THEMES AND SUB-THEMES

Meta categories	**Themes**	**Sub-themes**
Nonadherence	Unintentional nonadherence	Forgetting
		Hard to swallow tablets
		Vomiting up tablets
		Accidentally taking too much
		Accidentally taking too little: dropped tablet
		Prescribing error
		No imatinib available at pharmacy
		Frequency of unintentional nonadherence
	Intentional nonadherence	*Because of* side effects
		Because of socialising/dining out/drinking alcohol
		Because of travelling
		Because of diversion from planned activities

	Because of temporary illness (bug/cold)
	Because of risk of pregnancy
	Because of negative emotions and feelings
	Because of "no real reason/lack of discipline"
	Because of bad taste
	Changed doses
	Frequency intentional
	Contemplating future nonadherence
	Experimentation
Overlapping Intentional and Unintentional nonadherence	*Because of* bad taste
	Because of tiredness
	Because of first forgetting then could not be bothered
Consequences of nonadherence	Perceived consequences
	Conflicting information re consequences
	"Getting away with it"

		Reliance on monitoring and HCPs to detect and relay changes in clinical parameters
		Don't think missing the odd dose make a difference
	Action taken by patients in response to nonadherence	Compensating for missed doses
		Do not compensate for missed doses
		Changing routine to avoid nonadherence
	Positive reinforcement	
	Influence of trial procedures on nonadherence	
Adherence	Reasons for being adherent	Because the Dr says so / conformist
		Do not experience side effects
		Faith in HCPs / imatinib
		Understanding of how illness and treatment works
	Awareness of HCPs desire for adherence	
Medication management	Change over time	Becoming relaxed with taking imatinib as responding well

No change over time	
Strategies for taking imatinib	Strategies to manage side effects
	Routines
	Prompts
	No strategy

2.4.3 INTERVIEWS RESULTS: NONADHERENCE

In line with previous research, the results showed that patients reported both intentional and unintentional reasons for not adhering as prescribed (WHO, 2003, Nunes et al., 2009). In some cases the same patient described instances of both intentional and unintentional nonadherence, and at times intentional and unintentional reasons overlapped. Patient also gave examples of experimenting with their treatment regimen to better fit their circumstances and at times patients underestimated the impact their nonadherence could have on their response. This underestimation was partly due to feedback the patient had received from health care providers (HCPs). These findings are presented in detail below.

2.4.3.1 UNINTENTIONAL NONADHERENCE

Unintentional nonadherence, when the patient may want to take the medication but is unable to, was at times due to internal reasons, such as forgetting, and at other times due to external reasons such as prescribing error. The most common unintentional reason for not taking a dose was forgetting, which 13 patients gave examples of.

> ...And sometimes you just forget. It's very strange...//... It's almost a surprise when you don't take it... [Patient 07: line 97]

Patients mentioned a range of different factors that could cause them to forget taking a dose of imatinib, including distraction or changes in the daily routine (driving the wife to work). At other times, patients experienced problems with remembering whether a dose had been taken or not because the behaviour was automatic, in the same way as many of us forget whether we locked the house door or not, or whether we switched off the iron. This could also lead to unintentional overdosing with imatinib.

> ...I'd also worry about doing two lots on one day...//... I took them, and then half an hour later I took them again. I had a mental block for some reason... [Patient 19: line 62]

Even though some patients said they could not understand how anyone could forget to take the imatinib when their life depend on it, other patients acknowledged that it is "normal" and that most people will at times forget a dose.

> ...You know, everybody's going to forget to take it at some point, I don't think there's a hundred percent fail-proof way of remembering to take it every single day... [Patient 19: line 92]

These internal reasons of forgetting contrasted with external reasons, for example, one patient could not get the prescription dispensed at the pharmacy and was therefore not able to take any imatinib for a longer period.

> ...[the pharmacy] had no medication for me, so I went for nearly a week with no medication... [Patient 18: line 41]

Finally, some patients expressed physically not being able to take the tablets. Two patients had early on in their treatment regimen not been able to swallow the imatinib tablets. One of these patients, who had previously crushed the imatinib and mixed with water to drink, had less problems swallowing since the tablet size had been reduced. The other patient had learned to take the tablets by chewing it. However, this led the patient to at times choose to not take the imatinib because of

the bad taste. Thus an unintentional cause of nonadherence had prompted intentional nonadherence.

Other patients expressed at times getting nauseous and vomiting the tablets back up almost immediately. When this happens the patient is recommended by the HCPs not to take a second dose. Consequently, part of the dose could be considered missed as most likely the tablets would not have had time to get properly absorbed. Again, this type of unintentional cause of nonadherence had over the years led many patients to intentionally decide to not take the imatinib at times when they thought they would experience nausea.

2.4.3.2 INTENTIONAL NONADHERENCE

Intentional nonadherence, in which the patient decides not to take their medication as prescribed, was mentioned by 10 patients. In many cases the patients' reasons were to deal with side-effects, such as nausea, tiredness and lack of energy.

> ...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 them. I sleep better when I don't have it. So I consciously didn't take it. Because I didn't want to take it... [Patient 11: line 50]

In addition, many patients did not take their imatinib if they were going out to socialise with friends. Again this was mainly due to side effects, even though somewhat more indirectly because of possible interaction with alcohol or because of inconvenience of not being able to take imatinib in accordance with the normal routine. There might be some conflict of how to take late tablets if, for example, the imatinib is normally taken with food.

> ... I fancied a few beers, so I thought I won't bother, cause it makes me sick if you have alcohol with it, I noticed, so I didn't bother taking them... [Patient 21: line 53]

> ...So if we've been out and we've come back later than expected, say eleven o'clock at night, I am not about to go and have a couple of rounds of sandwiches just to take the tablets... [Patient 20: line 64]

Two other patients gave examples of choosing to not take the imatinib when travelling with work or when going on holiday.

> ...There's the time zone thing, and you just think you don't want to take it when you are travelling...//... It just seems to be more of a logical thing not to... [Patient 07: line 113-119]

> ...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, so you are talking about ten days... [Patient 17: line 113]

The two examples are different in that patient 07 reasoned that it is better to skip a dose when time zone differences make it difficult to take the imatinib at the "normal" time. In the case of patient 17 the reason for not taking the imatinib when travelling was to reduce side effects and thus being able to fully enjoy the holiday.

It is clear that the imatinib tablets are not easy tablets to take because of the many side effects and the routines patients form to deal with the adverse effects. A general perception from having spent time in the company of HCPs working with CML patients during the time of conducting these interviews is that that they do not take the adverse effects of imatinib and the impact this has on the patients' lives seriously enough. They seem to think that patients should be able to cope well with side effects of imatinib, because the alternative is worse; both in terms of previous treatments and in terms of the inevitable progression of CML if left untreated. Imatinib has indeed less adverse effects than previously used anticancer treatments for CML, such as interferon-alpha. In particular, the adverse effects of imatinib are much less, in comparison to the adverse effects associated with bone marrow transplant and immunosuppressant therapies, which was previously the

only long term treatment for CML. However, whether the alternative is worse or not, this knowledge alone is unlikely to help patients cope better with the side effects they do experience (except for possibly the patients who have experienced previous treatments and can appreciate the difference).

There were examples of more isolated causes of occasional intentional nonadherence, which again was indirectly caused by adverse effects of imatinib. For example, a female patient stopped for two weeks when she thought she might be pregnant, but never told her clinician about it. Intentional nonadherence also includes changing dose without consulting a clinician. The following quote come from a patient who experimented with trying out a lower dose to deal with side effects whilst being ill with the flu.

> ...I had a sort of fluey, buggy, thing...//... I was just taking [imatinib] and literally being ill...//... so I did try dropping the dose down, but it didn't make any odds, so I did stop taking it for about a week then... [Patient 17: line 71-73]

The abovementioned quotes, both from this section on intentional nonadherence and the preceding section on unintentional nonadherence, show that patients are either unintentionally or intentionally not taking doses of their imatinib. However, at other times the distinction is less clear and intentional and unintentional reasons for nonadherence seem to overlap.

2.4.3.3 OVERLAPPING UNINTENTIONAL AND INTENTIONAL NONADHERENCE

At times, intentional nonadherence overlapped with unintentional nonadherence, such as remembering later than the normal time point of taking imatinib that a dose has been missed and at that point making the decision not to take the imatinib.

...You remember you haven't done it, you feel – oh I can't be bothered tonight, it's not going to kill me [to miss a dose] – sort of thing, so I just go to sleep... [Patient 21: line 212]

As mentioned earlier, patients also expressed ways of dealing with unintentional nonadherence of not being able to swallow tablets, which in turn led to intentionally deciding to not take doses of imatinib because of bad taste. In one case the patient experienced continuous swallowing difficulties and therefore chewed the tablets. He had been told by the doctors that it is alright to chew the imatinib as the most important thing is that the tablets are ingested one way or another. The other patients used to experience swallowing difficulties when imatinib was given as larger tablets and used to have to crush the imatinib, stir them into a glass of water and drink it. This would in turn taste very bad leading to the patient choosing to not take the imatinib. However, since then the tablets are smaller and swallowing has become less of a problem for this patient (although the patient is still acknowledging missing several doses per week).

In a similar way to how the patient may work out ways to modify the way they self-administer their treatment (such as chewing or crushing tablets), other patients experiment with doses and treatment interruptions, just to see what happens.

2.4.3.4 EXPERIMENTATION

There were two examples of patients experimenting to figure out effects of the imatinib, both in terms of effectiveness and in terms of side effects. The first patient stopped the treatment for 2 months to see whether the clinical response would be affected. However, even after it was obvious the clinical response was affected by the nonadherence (the patient had to be confronted by several HCPs before acknowledging having stopped taking the imatinib), the patient is still reporting to miss several doses per week.

....In a way I was a bit, I thought, not that I wanted to see how long it would going up, but it was interesting to find out within two months [my PCR

> results] started going up ...//... obviously if you take it every day it is going to bring [my results] down and it is coming back down, but then I have to do what I feel is right for me... [Patient 02: line 274/616]

The other patient (who was adherent according to the clinical trial MEMS readings with adherence >90%) did not experiment with the actual treatment regimen, but was instead trying to work out what other life style factors may aggravate the side effects. In addition, the patient also wanted to figure out whether the side effects were adverse effects of the imatinib or whether the "side effects" were in fact symptoms of the CML.

> ... I have tried to work out whether [the fatigue come on] after any particular form of exercise or cause if I've been to the gym I might be dehydrated or whatever...//... but that's another part I do not like about, whether it is my condition or the Gleevec I don't know... [Patient 3: line 131-133]

The two abovementioned examples of patients experimenting to figure out effects of the imatinib is in line with theories based in a "common sense" understanding of illness and treatment, which may influence the way patients take and adapt their treatment regimen (e.g. Leventhal et al., 1992, Weinman et al., 1996). However, it is worrying that patients often seem to underestimate the consequences that their nonadherence can have on their clinical response.

2.4.3.5 PERCEIVED CONSEQUENCES OF NONADHERENCE

The consequences of nonadherence perceived by patients were different from those one would expect to find in HCPs. HCPs are probably more likely to think about the negative consequences of missing doses such as reduced clinical response. In contrast, the patients may instead perceive positive consequences of missing doses. For example, many patients do not perceive symptoms from the CML, but may instead experience side effects from the imatinib; thus when they are not taking the imatinib the side effects are reduced so they feel better if they do not adhere.

> ...I really noticed it when I didn't take it for 2 months...//... I felt myself again... [Patient 02: line 576-578]

Patients did show an awareness of the importance of taking the imatinib and of course they understand that the prescribing clinician's aim is that the patient takes the imatinib as prescribed. The quote below highlights the lack of communication between HCPs and patients regarding adherence to therapy.

> ...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. I think the assumption is this is your medicine, you have been prescribed to take at this rate per day, you know, it's up to the patient to take responsibility for that... [Patient 20: line 90]

However, a patient mentioned that clinicians tend not to notice if you have been nonadherent and "you get away with it" [Patient 2: line 302].

Furthermore, many patients thought that missing a few doses will not affect their clinical response. Twelve out of twenty-one patients stated that they did not think missing "the odd dose" would make a difference to their response to imatinib.

> ...I am comfortable that if I know I miss the odd dose now and again it is not having a detrimental effect over a long time ...//... So I don't feel I am putting myself in any danger by not taking an odd dose now and again... [Patient 09: line 50]

However, patients' may not be very accurate in estimating the extent of their own nonadherence. For instance, a patient said:

> ...My view, rightly or wrongly, is I know I've done it for years [being nonadherent], and I seem to get the impression that I'm not alone, and as long as I take 95 percent of the time, a tablet, then I get the impression I'll still be controlled rather well... [Patient 12: line 45]

Simultaneously, the same patient admitted to having missed doses in the last 7 days, to miss 3-4 doses per month and was found to have had MEMS adherence <90%. This information combined indicates Patient-12 overestimates his adherence rate and is in fact most likely to have an adherence rate less than the 95% stated. In addition, in two cases the patients spoke openly of their own nonadherence during the trial. One patient said he has no idea how many doses he missed during the trial, but that his guess was about 2 [Patient 15: line 90]. In fact the MEMS had recorded 10 missed doses. The other patient said that even though he knew he was missing doses he was surprised to realise that he had missed as many as 20% during the trial [Patient 11: line 35].

It seems as if many patients build a mental "model" of how their illness and treatment work and to a certain extent base their behaviour and decisions on this model, which may not always be correct. This is again similar to that proposed by the common sense models of illness (e.g. Leventhal 1992, Wienman 1996). For example, some patients believed that clinical outcome will only be negatively affected if they miss the imatinib many days in a row. The reason for this appears to be that patients believe that the imatinib builds up in the body and that it takes longer than a day or two for the drug to reach damaging low levels.

> ...I believe you still have a lot of the medicine in your body system. So I think you are still topping up, keep topping up, if you've missed three, four days, then I don't know... [Patient 10: line 88]

Another patient reasoned:

> ...I guess it must, if they say take 500mg a day and I am missing ten percent, that is effectively only 450 a day, is that enough to make a difference? I don't know... [Patient 20: line 86]

This is consistent with findings that patients in general show a motivation to minimise intake and that most strategies used by patient to modify their treatment

regime is to do just that (Pound et al., Nunes et al.). Indeed, even adherent patients expressed an interest in the possibility of reducing doses:

> ... Obviously if you have a reduced dose then you have less toxicity going into the system, so therefore that would be desirable. I don't know how much work has been done, if you normally have 400, whether you could get away with 300, in other words what does that do to the PCR count and all the rest of it?... [Patient 1: lines 157-159]

Nevertheless, some patients stop for longer periods and still think there will not be a negative effect on their outcome long term. In some cases the patients rely on the imatinib to work well as soon as they start taking it again.

> ...I know it's not good...//... if I don't take it, but I know I can control it with [imatinib] again, as soon as I start taking it... [Patient 13: line 103]

Of course, as with the individual perception of what constitutes an "odd dose" so patients' perception of "long term" may also differ. The following patient does not seem to consider a full month of not taking imatinib, also known as Gleevec, as "long term".

> ...I've only stopped taking Gleevec for, like, a month. A couple of times, just one month. And obviously that didn't make any difference [in clinical response]. So the question is what would happen if I stop taking it long term?... [Patient 16: line 38]

In essence, nonadherent patients tend to rely on clinical parameters to detect adverse consequences, or to trust that their clinician would let them know if there are any adverse effects detected. This suggests that the patient's rationale of how the drug works and the perceived consequences of nonadherence, in combination with input from the clinician may influence the behaviour whether to take the medication or not.

> ...I check my result every time I come here, so if they're still very good then I can't see as if I've done anything wrong... [Patient 04: line 729-731]

> ...I suppose if they noticed that there was something wrong then they would say, you know, make sure you take the full dose... [Patient 09: line 56]

This possible influence that clinicians can have on patient behaviour highlights the importance of having open and honest discussions about both negative and positive clinical feedback. However, it is also possible that this is the patients justifying missing doses, possibly both to themselves and to others. In particular, as even when patients seem aware of their PCR results changing they seem unsure whether this is actually related to the way they take their imatinib or some other unknown factor.

> ...Well, I don't know whether, I might have been not so good taking them in the past, and whether that's coincidental or not that my PCR has come down over time, as I have got better not missing doses. ...//... Maybe it is the fact that I have been better, stricter, at taking it as prescribed, has maybe led to the PCR coming down... [Patient 20: line 86]

Naturally it is always difficult to draw definite conclusions of what are the causative factors, as with any research question. This example of a patient trying to work out how adherence has influenced clinical response is in line with common sense based theories of illness related behaviour (e.g. Leventhal 1992). These theories suggest that patients appraise internal (e.g. symptoms) and external (e.g. information) feedback about their illness and treatment and this appraisal may in turn influence their behaviour.

It is interesting to note that in the case of CML patients taking imatinib the perceived internal feedback of the effect/consequence of nonadherence may often be perceived as positive as side effects are reduced. This is particularly noticeable when the patients have not experienced symptoms of the CML before diagnosis. In addition, other patients mentioned that the side effects of imatinib were identical

to the symptoms of the CML. This implies that it may be hard for patients to distinguish whether a perceived adverse effect is side effects of the imatinib or symptoms of the CML and in either case missing doses would result in feeling better.

The external clinical feedback, in contrast, has the ability to act as a feedback loop where negative consequences of nonadherence can be detected by the health care provider and, if communicated appropriately, perceived by the patient. The patients seem to reason that if their behaviour is causing problems their clinicians would tell them and as long as the clinicians do not do so their nonadherence must be "safe". Even though feedback of negative consequences of nonadherence would not directly influence the patients to increase the adherence level, at least it places the patient in a better position to decide whether to still miss doses, despite adverse effects on clinical response (but possible better quality of life), or to try and improve adherence. However, from the interviews it appeared as if the clinical feedback the patients had received from health care providers often had reinforced their nonadherent behaviours, rather than increased adherence.

2.4.3.6 POSITIVE REINFORCEMENT OF NONADHERENT BEHAVIOURS

The interviews suggest that patients are reinforced in their nonadherent behaviour by certain types of feedback from the health care system, in particular through communication with HCPs, but in one case through information leaflets. Twelve out of twenty-one patients made comments in relation to receiving feedback that seems to have reinforced the belief that "occasional" nonadherence does not matter. Two of these patients had a MEMS adherence rate >90% and were thus considered adherent. Of course, "occasional" nonadherence defined as missing doses very rarely, say once every second month, is unlikely to have an effect on response. However, patients varied greatly in what would constitute an "occasional" or an "odd" dose missed; in many cases more than 3 doses missed per month were still considered "occasional" or "odd". Three doses in 1 month are

already 10%, which we know is the cut off point for a nonadherence rate that is likely to influence the clinical response negatively.

A key example of this positive reinforcement of nonadherence was that after communication with HCPs several patients felt reassured that their nonadherence would not have a detrimental effect on their response.

> ...[the pharmacists] said - look, we just had a chat with the doctors and they've said it doesn't matter if you missed a weekend, it's absolutely fine... [Patient 14: line 94]

> ...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... [Patient 21: line 79]

Nonadherent behaviours also seemed to be reinforced when patients have been off imatinib for a period of time for some reason, and they themselves perceive that this treatment break did not have a detrimental effect on their response.

> ...Well, I stopped taking it, to conceive [my child], and then I was off it for like seven months, and nothing seemed to happen for seven months...//... So I thought - blimey, I'm off it all this time, and actually it's not making a lot of difference... [Patient 11: line 144]

The patients seemed to have a belief that their clinical responses have not been affected by their nonadherence. Hence, it could be inferred that clinicians tend to relay feedback on clinical response in a positive light by focusing on results that are positive. In the previous section it was argued that clinical feedback could constitute a feedback loop where patients receive external feedback regarding their clinical response, which may be important if there is a decline in clinical response that has been caused by nonadherence. This suggests some rethinking is needed in practice regarding how to relay clinical feedback to CML patients. It is possible that more frank communication regarding clinical response would

support adherence in this patient group (although this is not necessarily the case as clinical feedback on treatment response in HIV patients is perceived as less important by patients when evaluating their treatment than their subjective experience of their health and symptoms (Pound et al.))

Finally, one patient referred to the imatinib information leaflet as another source of information that may have reinforced nonadherent behaviour.

> ...I wouldn't have thought it would have had that major impact [to miss a few doses]. I mean, reading the paperwork you get with the tablets, it says take it as soon as you realise, and just get back into the routine... [Patient 10: line 88]

The information leaflets advise patients what to do when having missed a dose, assuming that the dose has been missed unintentionally. Indeed, patients mentioned different ways to deal with missed doses, which will be discussed in the following section.

2.4.3.7 BEHAVIOUR BY PATIENTS IN RESPONSE TO NONADHERENCE

Patients discussed during the interviews what they would do if they had unintentionally missed doses of imatinib. Two patients experienced frequent unintentional nonadherence at the early days of treatment, and therefore responded by seeking out adherence aids to help improve their adherence, which will be further discussed in section 2.4.3.1 on strategies for adhering to imatinib. The most common response to deal with unintentional missed doses, which 8 patients mentioned, was that they would simply take the next dose at the correct time and these patients would not compensate by taking the missed dose at a later stage. Only two patients said that they would take the missed dose in the morning the day after having missed a dose, or spread out the dose by taking a few smaller doses throughout the day (imatinib comes in either 400mg or 100mg formulations, and only patients prescribed their dose in several tablets can easily spread out their dose over the day), and then take the normal dose in the evening.

> ...But I wouldn't then take five hundred milligrams in one go because in the morning I just feel sick, so probably two hundred, two hundred lunchtime, and another hundred at another point ...//... I would have my normal dose in the evening, but as late as I possibly could then... [Patient 13: line 64]

Two patients mentioned that they would consider changing their current routine of taking imatinib, to possibly improve their adherence, as a result of discussing their adherence during the interviews. This suggests that guided reflection of adherent behaviours may lead to behavioural change and highlights an area that may be worth exploring when developing adherence enhancing interventions.

> ...That's probably the routine that I might change...//... I can manage more when I eat, I might start to take them in the morning. Because then you've done it for the day. So it means having a significant breakfast. If you've taken the tablets you can then forget about it, even if you don't eat for the rest of the day it doesn't really matter...//... So maybe I should consider changing when I take them... [Patient 20: line 64-66]

The abovementioned quote is an example of how research methods (in this case interviews) may influence patients' subsequent behaviour. However, during the interviews there were also several issues that emerged in terms of the possible influence of the clinical trial research methods on patients adherence, or on their recorded adherence rate, will be discussed it the following section.

2.4.3.8 INFLUENCE OF RESEARCH METHODS ON RECORDED NONANDHERENCE AND NONADHERENT BEHAVIOURS

Five patients with MEMS adherence <90% mentioned issues relating to the trial that could have influenced their adherence or influenced the adherence rate that was recorded during the trial. For example, four of these 5 patients, who all had a MEMS adherence rate below 85%, claimed during the interviews to never miss any tablets. There are several possibilities for this discordance between MEMS adherence rate and self-report. First of all, it is possible that the patient did not

want to report nonadherence in the interview. Secondly, it is possible the patients reported to the best of their knowledge that no doses had been missed, but in reality had forgotten to take the imatinib without later realising a tablet had been missed, i.e. that the patient had forgotten that a tablet was forgotten. Finally, it is possible that all or some of these four patients are telling the truth, and that the MEMS data instead have been incorrect. For example, two of these four patients claimed to always carry a few imatinib tablets on them. Both patients might have done this throughout the clinical trial and therefore sometimes not taken the imatinib from their MEMS bottles, which would have been recorded as a missed dose.

> ...I always carry some of the Imatinib around with me in my wallet, which means that when I finish dinner, at that point, I take the Imatinib... [Patient 14: line 135]

> ...I literally have this pot *(she is taking it out from her bag)*, and it has seven doses in it, and it's always with me... [Patient 16: line 154]

Two other patients who normally were using monitored dosing boxes reported difficulty during the trial as they were not allowed to use this adherence aid during the trial. One patient admitted to have used the monitored box for a few days during the trial, but stopped because he perceived the imatinib to have changed colour and drew the conclusion that the air damage the imatinib tablets (normally he would cut apart the blister pack so that the imatinib would be protected from air in the monitored dosing box). It is therefore possible that this patient influenced the MEMS reading and was presumed to have missed doses during the days the MEMS bottle had not been opened, when in actual fact doses had been transferred and ingested from the dosing box. The same patient also reported difficulty in taking the imatinib during the trial period. Another influence of the trial methods could therefore have been that this patient has a somewhat better adherence to the prescribed treatment outside of the trial conditions.

> ... I did this 3 months study and I couldn't put it in my little compartments. I did put it in the start in my little Monday, Tuesday, Wednesday box, but they seemed to fade a bit, so I stopped doing that...//... So I had to take them all out, count them, see how many I had, work out how many I should have left, and if I'd missed one I took it... [Patient 10: line 78-88]

A more positive consequence of the trial, reported by one patient in the interview, was that the trial results opened up a discussion between the patient and the prescribing clinician about the patient's adherence and clinical response, which resulted in a possible improvement to the patient's subsequent adherence to imatinib. It appeared as if the trial had made the prescribing clinician responsive to the patient's experiences of taking their imatinib treatment. During the discussion side effects were identified as the reason this patient choose not take the imatinib several times per week. Consequently, the clinician reduced the patient's dose from 600mg to 400mg, resulting in decreased side effects and the patient is thus trying to take the tablets as prescribed. The patient expressed being motivated by knowing that the chance of achieving a good response on the lower dose is increased with better adherence.

> ... I knew I was missing days, but I didn't quite realise how many I was missing. So it worked out that maybe I'd missed twenty percent of the doses over a three month period. So it wasn't working quite as well as it could do, so they said – we'll bring your dose down instead, to 400mg, make sure you take it every day. And the side effects haven't been quite so bad. So it's more manageable to do that... [Patient 11: line 35]

The above quote is a very good example of involving patients and their experience into decisions about their treatment as proposed by recent policy guidelines (DoH, Nunes et al.); in particular as the patient expresses a motivation to now adhere better to the imatinib.

As was previously mentioned, it is evident that MEMS readings can be biased by the patients' behaviour. In other cases the trial can end up having a positive effect

on patients' subsequent adherence. It may also be beneficial to explore how some patients do achieve adherence to increase our understanding of adherence behaviours in general, which will be the focus of the following section.

2.4.4 INTERVIEW RESULTS: ADHERENCE

2.4.4.1 REASONS FOR BEING ADHERENT

Sixty-four patients (74%), of the total clinical trial sample of 87, were considered to be adherent with a MEMS adherence rate above 90% (Marin et al. 2010). Four of these adherent patients were interviewed. Two patients experienced side-effects and still took the imatinib as prescribed despite periods of severe fatigue, which had prompted changes in everyday activities and contributed to tensions with family and friends. In both cases the patients referred to being conformists who do what the doctor prescribes. One of the two patients said the reason for following the doctors' prescription is because of a great trust in the clinician who oversees the treatment plan.

> ...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]... [Patient 03: line 164]

The same patient discussed a general aversion since a young age to take any type of medication, and therefore found it a challenge to get over this "hurdle" and start taking the imatinib every day. However, once over the hurdle it became a routine to take it every morning. In addition, the patient pointed out that tablets are a much easier formulation to take every day instead of "drinking an elixir or have something put through your veins" [Patient 03: line 71]. Thus, it is clear that even the adherent patients at times have a mixed perception of the imatinib. This mixed perception was perfectly illustrated by the patient referring to imatinib with the oxymoron: "it's a wonderful poison" [Patient 03: line 453]. Other adherent patients also experience this internal tension regarding adhering to the imatinib treatment:

> ...I wonder myself whether I am doing the right thing, taking these flipping tablets, they make me feel so ill... [Patient 08: line 145]

The other two adherent patients did not have any side effects, and therefore did not see any reason to not take their imatinib.

> ...[My side effects are] extremely marginal, nothing which you would regard as being an incentive to want to stop taking the medication... [Patient 01: line 93]

This quote again highlights that appropriate management of side effects may be the key to facilitating adherence in CML patients prescribed imatinib. Indeed, patients mentioned many strategies that were used to manage their imatinib treatment, which will be discussed in the following section.

2.4.5 INTERVIEW RESULTS: MEDICATION MANAGEMENT

2.4.5.1 STRATEGIES FOR ADHERING TO IMATINIB

The four adherent patients, with MEMS adherence >90%, all referred to taking their imatinib as being a part of their daily routine "like cleaning your teeth or combing your hair" [Patient 08: line 127]. One patient referred to the morning routine as the perfect time to fit in the medicine taking, as the evening routines generally are much more open for change and interference. Three patients mentioned some sort of prompt that reminds about taking the imatinib, for example, taking the imatinib with a meal, or to leave medicines out in the living room as a visual prompt, or a partner who reminds them:

> ...[my wife] is quite good at nagging me in terms of taking the medication, so that is quite a good prompt... [Patient 01: line 55-57]

Furthermore, the patients who were found to have MEMS adherence ≤ 90% in the clinical trial (Marin et al. 2010), and thus considered nonadherent, also mentioned

forming routines, getting into habits and using prompts to facilitate their adherence to imatinib.

> ...It's just habit, get up, having breakfast and take the pill... [Patient 17: line 93]

The quote below also illustrates how in making the Simpsons (a cartoon TV program) the prompt for taking the imatinib the treatment regimen has become part of a family event, which also involves the children.

> ...Six o'clock every night, you know, the Simpsons on – "mum take your tablet" .../.../... we used to say six o'clock, when the Simpsons comes on that's mammy's tablet, it makes mammy special... [Patient 18: line 86-88]

Several patients, both below and above 90% MEMS adherence, mentioned the importance of planning forward to take imatinib with them when going out or going on holiday.

> ...if I go out, then I always take a tablet with me... [Patient 01: line 81]

> ...Obviously holiday, [imatinib is] the first thing that I pack... [Patient 18: line 120]

Five patients described using adherence aids. Four of these patients would normally use monitored dosing boxes, such as Dosette boxes, which have little compartments for each day of the week to help with keeping track of taking the imatinib. All of these patients had MEMS adherence under 85% in the trial, and two also admitted to have missed a dose in the last 7 days.

> ...[the dosing box] doesn't necessarily help me to remember, but it makes me realise if I've missed any... [Patient 11: line 77]

Two patients, with MEMS adherence under 85%, used alarms to help remember to take the imatinib on time; one of these patients used it in combination with a monitored dosing box. The patients who used dosing boxes were asked to not use

it during the clinical trial, but to take their medication directly from the MEMS bottle. Therefore, it is possible these patients would have a better adherence rate normally when they are using their monitored dosing boxes.

As mentioned previously in section 2.4.3.1 and 2.4.3.3, two patients had experienced problems with swallowing the imatinib tablets, one of them resorted to chewing the tablets and the other to crush and dissolve the imatinib in water to drink. One of these patient has ongoing problems with swallowing and the other patient only had swallowing problems when previously having been prescribed larger tablet formulations.

Eighteen out of the 21 patients interviewed mentioned strategies they used to deal with side effects of imatinib. Ten patients mentioned using "safe foods", which is food or drink taken in combination with the imatinib to reduce side effects such as nausea (from the interviews, as well as the patient feedback session reported below, it seems that carbohydrates in particular reduce nausea, but I have not been able to find any evidence supporting carbohydrates in particular reduce nausea side effects of imatinib). The discovery of specific "safe foods" that work better than others in reducing nausea seems to have been figured out by the patients themselves, as there is no mention in the literature of specific foods reducing nausea associated with imatinib; although some clinicians may recommend patients to take the imatinib in combination with a meal to reduce nausea.

> ...I call them safe foods so if I eat certain food I know I won't get as bloated or I won't get the nausea... [Patient 03: line 178]

Four patients mentioned taking the imatinib right before going to bed in order to fall asleep before the nausea arises.

> ...I take it before I go to bed, the five hundred milligrams with a glass of water, and fall asleep, so I never have any illness, sickness, or ever feel odd... [Patient 13: line 54]

Other ways in which the patients had dealt with side effects included not mixing intake of imatinib with alcohol consumption, splitting the dose and instead take half the dose twice per day, and in two cases the patient's dose had been reduced by the prescribing doctor in order to reduce the severity of side effects. Some patients had been prescribed or recommended co-therapies to reduce side effects such as anaemia, muscle cramps, skin reactions and nausea. However, there was one example where a patient might have misremembered the consultant's instructions of how to deal with muscle cramps, which can be treated with quinine (which can be found in small amounts in tonic water); or alternatively the consultant has indeed given the patient incorrect advice. It is interesting, but worrying, to see that even though the patient expresses disbelief over the consultant's recommendations the patient accepts that the instructions *must* be correct and has therefore not verified the correctness of the instructions with her HCPs.

> L: Do you have any extra medicines that they give you for cramps, for example?
>
> P: No, they told me to drink, it's just crazy, it's Dr Pepper.
>
> L: Really?
>
> P: Yeah, there's quinine or something in the Dr Pepper, but obviously I like my Coke, I am literally Coke mad, I have to have my Coke daily, and I've checked the Coke and checked the Dr Pepper. There's no difference in the ingredients. So I don't, I stick to my Coke. But no, one of the consultants at [my local hospital] said to drink Dr Pepper... [Patient 18: line 131-134]

Eight patients, both adherent and nonadherence patients according to the MEMS readings, said that the side effects are a trade off for the response they achieve on imatinib.

> ...The few side effects I am getting, for what it's doing for me, I just think it's a no brainer. It's not even a trade off, it's just common sense to keep taking it... [Patient 17: line 214]

2.4.5.2 CHANGE OVER TIME OF MEDICATION MANAGEMENT AND ADHERENCE

Several patients stated that their adherence and the way they managed their treatment had changed over time. Although, five patients said there has been no change in the experience of taking imatinib over time, 13 patients had experienced some change over time. Five patients who experienced change said they were rigorous about taking the imatinib exactly as prescribed in the beginning, but started to miss tablets after some time.

> ...LE: In the last 5 years, when do you think you started to miss a few doses?
>
> P: probably after 6 months... [Patient 04: line 266-267]

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. Examples from patients included getting used to side effects, as well as fitting in imatinib treatment with daily life.

> ...Maybe in the very, very beginning, trying to get used to it, I maybe threw up a couple of times...//...It's always been hard when I've been off it, to go back on it. Psychologically and physically... [Patient 13: line 76-78]

One patient found the previous imatinib tablets very hard to swallow as they used to be a larger size, but with the new smaller formulation this problem had disappeared. Two patients used to be on higher doses, and had during this time found it hard to take the imatinib because of side effects. The doses had now been reduced, and both patients therefore experienced fewer problems with taking the tablets.

There seemed to be a tendency of patients reporting an increase in intentional nonadherence and a decrease in unintentional nonadherence over time. In particular, it is evident that some patients' intentional nonadherence tends to increase after the patients have been told they are responding well, as if they can

then afford to sometimes not take their imatinib without it affecting their response.

> ...I think I stuck to it more rigidly at the beginning, yes, I think so...//... And since, when you get into cytogenetic remission and molecular remission and everything, you sort of tend to breathe a sigh of relief in some ways, because you sort of think, OK, it's working... [Patient 19: line 85-87]

In contrast, for other patients the reason for not being able to adhere in the beginning of treatment was due to unintentionally forgetting. Consequently, some patients sought out adherence aids, such as monitored dosing boxes and alarms, and they found it helped to reduce their unintentional nonadherence.

> ...I got one of those, from Boots, little compartments, Monday, Tuesday, Wednesday, so that helped in the end, but before that it was always sort of a struggle to remember if you did take a tablet... [Patient 10: line 16]

The results showed that the way patients manage their imatinib treatment frequently changes over time. In some cases patients find it easier to adhere to treatment over time as a routine is formed, they get used to side effects and they might start using adherence aids to help remembering to take the imatinib. For other patients, nonadherence seems to increase with time. Often this increased nonadherence is due to the patient relaxing their rigour about taking the imatinib exactly as prescribed when the patients perceive they have responded well to the imatinib.

2.4.6 PATTERNS OF ADHERENCE AND NONADHERENCE

This section will present the patterns of adherence/nonadherence that was displayed by the 21 patients who participated in these interviews. When determining the different patterns both the narratives from the interviews and the MEMS patterns were analysed. The congruity of patients' narrative and the MEMS readings varied. In 11 cases they were considered mainly congruent [P1, P2, P4,

P6, P7, P8, P9, P11, P12, P17, P19 and P20), although patients at times underestimated their own nonadherence. However, in 7 cases MEMS and patient narratives were clearly *not* congruent [P3, P5, P10, P13, P14, P16 and P18). Even though this at times seems to be due to patients (with right) not wanting to report exact behaviour, this also raises some questions regarding the validity of the MEMS in measuring complex behaviours such as medication adherence. Details of the different patients' patterns, as well as, related similarities and disparities between MEMS and narratives, will be discussed in detail in the relevant sections below.

All the MEMS chronology charts will be displayed, but not the MEMS diary view, as it was thought that the chronology charts are the clearest display to highlight the different patterns. The patterns that were identified were as follows:

- The adherent
- The "random" occasional
- The "random" frequent
- The decline over time
- The good-decline-good
- The Dosette box users

2.4.6.1 THE ADHERENT

Four patients who were adherent were interviewed. Their adherence patterns from the trial are displayed in (Figure 10). Patent 08 and Patient 01 displayed perfect adherence, including that the final 3 doses before the clinical trial appointment was taken in the morning. Obviously Patient 08 was taking imatinib doses twice daily and Patient 01 once daily (the higher up in the chart the later in the day, midway of the Y-axis is midday 12am).

Patient 06 is interesting because it can clearly be seen that doses have been taken slightly later during the weekend than during the weekdays. However, during the

4th week of the trial, doses were taken at a similar time to the weekend, which may indicate the patient having time off work.

In the case of Patient 03 it can be seen that during 5 days the MEMS device has not been opened. However, in each instance the MEMS device has in fact been opened twice the day before, in each case later in the evening, although the patient reports to take the imatinib with breakfast. Patient 03 has an occupation where he at times needs to work night shifts. Therefore it is very possible that during the nights that he has to spend at work he takes out the tablets he needs for the following morning.

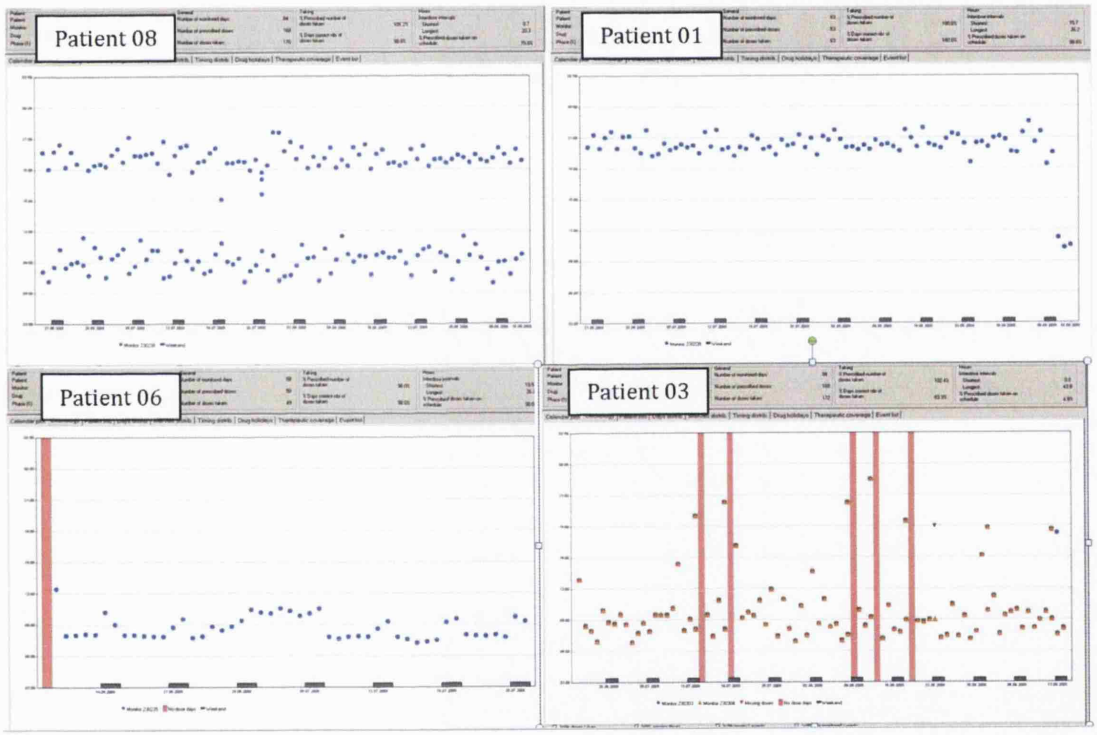

FIGURE 10 ADHERENCE PATTERNS: THE ADHERENT

2.4.6.2 THE "RANDOM" OCCASIONAL

The "random" occasional were the patients who missed less than 1 dose per week on average, but no particular pattern was apparent (Figure 11). Patient 15 said he found it a bit more difficult to know if he taken his imatinib or not during the trial

as he normally would keep the blister pack in a certain order to facilitate remembering if he has taken his tablets or not. He estimated that during the trial he might have missed about 2; in fact he had missed 10 doses. This highlights the possible impact that trial methods can have on patients' adherence, as well as the common finding that patients tend to underestimate their own nonadherence (DiMatteo, 2004b). Underestimation could either be a real difficulty in estimating own adherence rates, in particular when trying to estimate adherence rates during a period already several months in the past, or because the patient wants to appear more adherent.

Patient 16 claimed to never have missed any doses, except when having been off on the doctors' advice:

> ...I have never missed a dose, ever. I am probably the only person in your clinical thing who did not miss one single dose... [Patient 16: lines 55-58]

The grey areas in the chronology chart of patient 16 were periods that were not monitored and should therefore be ignored. The discrepancy between the patient's narrative and the MEMS recordings could be because the patient did not want to report instances of nonadherence, or it could be that doses have been taken from a second source. Patient 16 claimed to always carry a pot with 7 doses of imatinib in her bag, which she showed me during the interview, so that she always has doses at hand when it is time to take it.

Patient 17 was happy to talk about his nonadherence. He said he sometimes forgets and at other times he chooses not to take the imatinib, in particular the day after he has been out drinking. In addition, this patient stopped taking the imatinib for 10 days during last year's holiday and said he planned to do the same during the coming holiday.

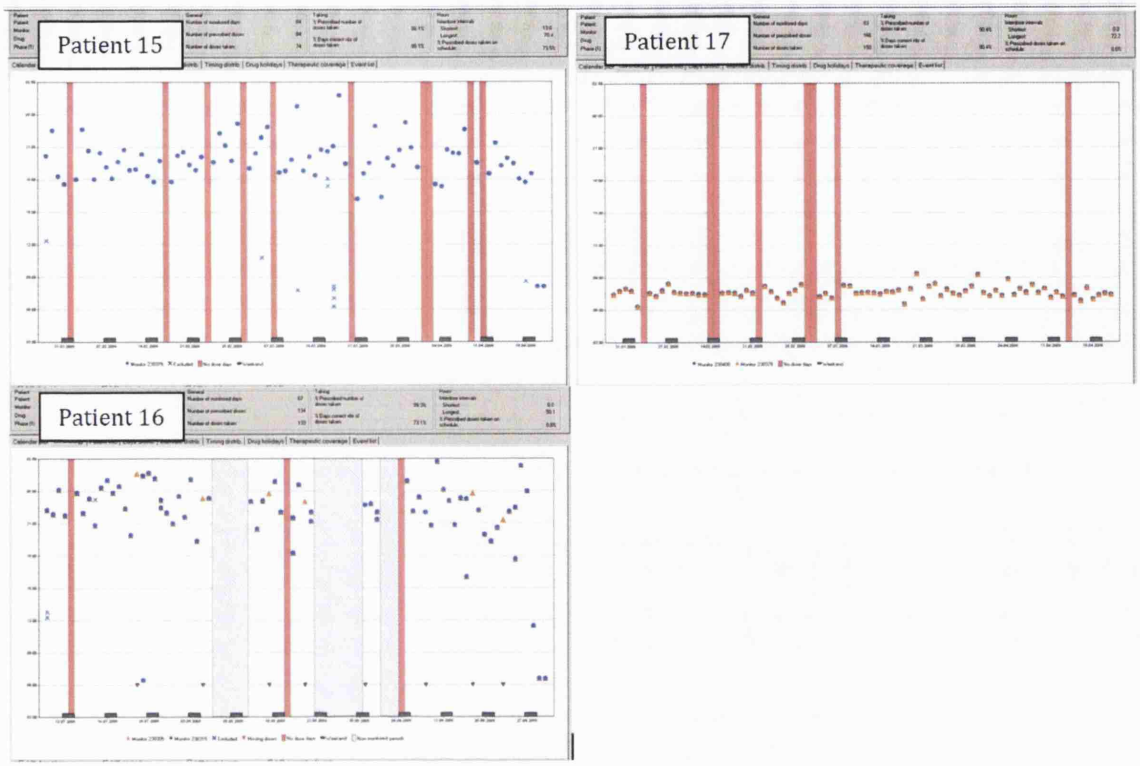

FIGURE 11 ADHERENCE PATTERNS: THE "RANDOM" OCCASIONAL

2.4.6.3 THE "RANDOM" FREQUENT

The "random" frequent were the patients who missed 1 or more doses per week on average, but where no particular pattern was apparent (Figure 12). The chronology charts show that Patients 02, 19, 11 and 21 usually took their imatinib at about the same time, when they took it; whereas Patients 04 and 14 have a wider spread of timings when the imatinib was taken. With the exception of Patient 14, all of these patients were intentionally nonadherent, and some mentioned to also forget at times, and all were happy to discuss why they were missing doses during the interviews.

Patient 04 missed doses intentionally to cope with fatigue and other side effects. He estimated that he missed about 3 doses per month, but from the chart it is apparent he missed more doses than that. As mentioned previously, it is several

months between the MEMS monitoring period and the interviews, so discrepancy can reflect a difficulty remembering correctly after this time gap.

Patient 02 also missed doses intentionally to cope with side effects, including fatigue, gastro-intestinal irritations and effects the imatinib has on her emotions and general feelings. She estimated that she missed about 6 to 7 doses in a month and she has previously stopped taking the imatinib without telling the doctors for 2 months. She also said she would do the same again if she felt she wanted to and she would not tell the doctors if she did.

> ...I think, it's my body...//...I have to do what I feel is right for me...
> [Patient 02: lines: 616-620]

Patient 19 talked openly about her nonadherence; at times she forgot and at times she decided not to take it. She also admitted to have missed one dose in the 7 days preceding the interview.

Patient 11 was happy to talk about his nonadherence. He generally missed doses to deal with side effects, such as fatigue and nausea, and because he did not think it would "make a big deal" if he missed one or two every now and again. He said he could miss up to 2 or 3 doses in a row, but was surprised after the trial to realise he missed as many as 20 percent. The patient also admitted to having missed one dose in the 7 days preceding the interview. However, he says since his dose had now been reduced from 600mg to 400mg, his side effects had been reduced and this one dose he missed in the last 7 days is probably the only one he has missed during the month preceding the interviews. Nonetheless, Patient 11 also mentioned normally using a Dosette box. However, because there was no apparent influence of the use of the Dosette box on the patterns of adherence or further themes from the interview that this patient had specific difficulties during the trial period, the adherence pattern displayed was grouped under as a "random" frequent patter. Therefore, it should be considered that it is possible the patient did display a higher nonadherence rate compared to normally.

Patient 21 says he might forget to take the imatinib once per week and decide to not take the imatinib once per week. When he chose to not take tablets it was usually because he had drunk alcohol. He said he used to be worried about missing doses, but was not worrying about it anymore as the doctors have told him it is not "life or death" if he misses a few.

Patient 14 says he cannot say for sure he has not missed any doses during the last 6 months (which would have included the MEMS monitoring period), but certainly not in the 7 days preceding the interview. He says he used an alarm watch which reminds him to take his imatinib, which was usually kept on a 'snooze' function so that it buzzes intermittently until he has taken the tablets; although the strap broke a few days so he was not wearing it to the interview. Nonetheless, the MEMS monitoring suggest that this patient was frequently nonadherent. This discrepancy could be explained by the patient not wanting to disclose nonadherence. This is consistent with the great variability of the dose timings, which suggest that he is not taking the imatinib when the alarm goes off. However, he also says he always keeps doses of imatinib in his wallet in case he is out when he should take a dose. Consequently, it could be that the doses that were recorded as missed were doses he had taken out from the MEMS device beforehand and ingested at a later time from the wallet. This could also explain the great variability in timings as he might have opened the MEMS device at the time of leaving the house, but only ingest the tablet at a later time when the alarm goes off.

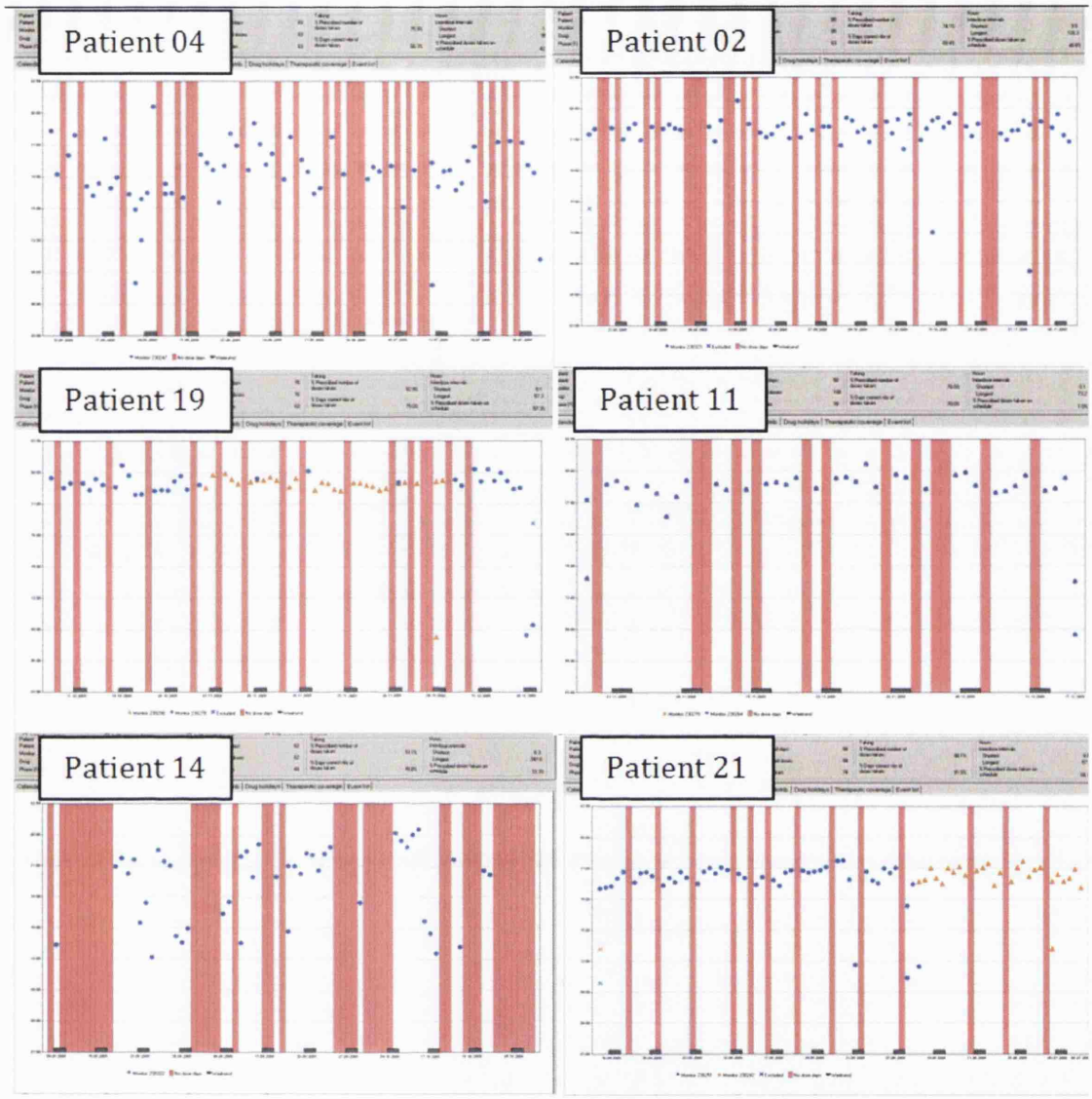

FIGURE 12 ADHERENCE PATTERNS:: THE "RANDOM" FREQUENT

2.4.6.4 THE DECLINE OVER TIME

The patients whose adherence rate declined over time showed a distinct pattern of missing an increasing amount of imatinib tablets over the monitoring period (Figure 13). This could be because they tried to improve their adherence after having been at the hospital; in particular as they were aware they were in a trial. However, after some time they seem to have fallen back into a routine of missing doses. Patient 09 talks openly about his nonadherence during the interview and

says that he most often forgets because of distraction, in particular when working or staying away from home. The charts show that he has missed both doses on many days, but also that he has missed one of two doses on many days, indicated by the small red triangles at the bottom of the chart. The patient admits to having missed 2/14 doses in the 7 days preceding the interview. He also is not worried about missing "the odd dose now and again", although he says he does not know what would happen if he missed a week in a row:

> ...If I stopped taking them completely for a week, who knows what would happen? I don't know, I've not been in that situation... [Patient 09: line 50]

However, the 8 final days of the MEMS monitoring period has recorded 8 days that the patient has missed doses. As mentioned previously, this could be because of the patient not wanting to disclose nonadherence, or could be that he has forgotten he missed doses or that he transferred the last 8 doses to a smaller container than the MEMS device.

Patient 07 was also happy to discuss his nonadherence, which can be due to forgetting or deciding to not take tablets because of having been out with friends, when travelling or when feeling a bit ill. He said that he had not missed any doses in the 7 days preceding the interview. It can be seen that the day before the 3 days in a row where the MEMS has not been opened there were two openings close together, which may indicate that doses were taken out to cover the weekend. However, this is only my interpretation and might not be the case. Patient 12 reported sometimes not taking his tablets as he had to chew them and he strongly disliked the taste.

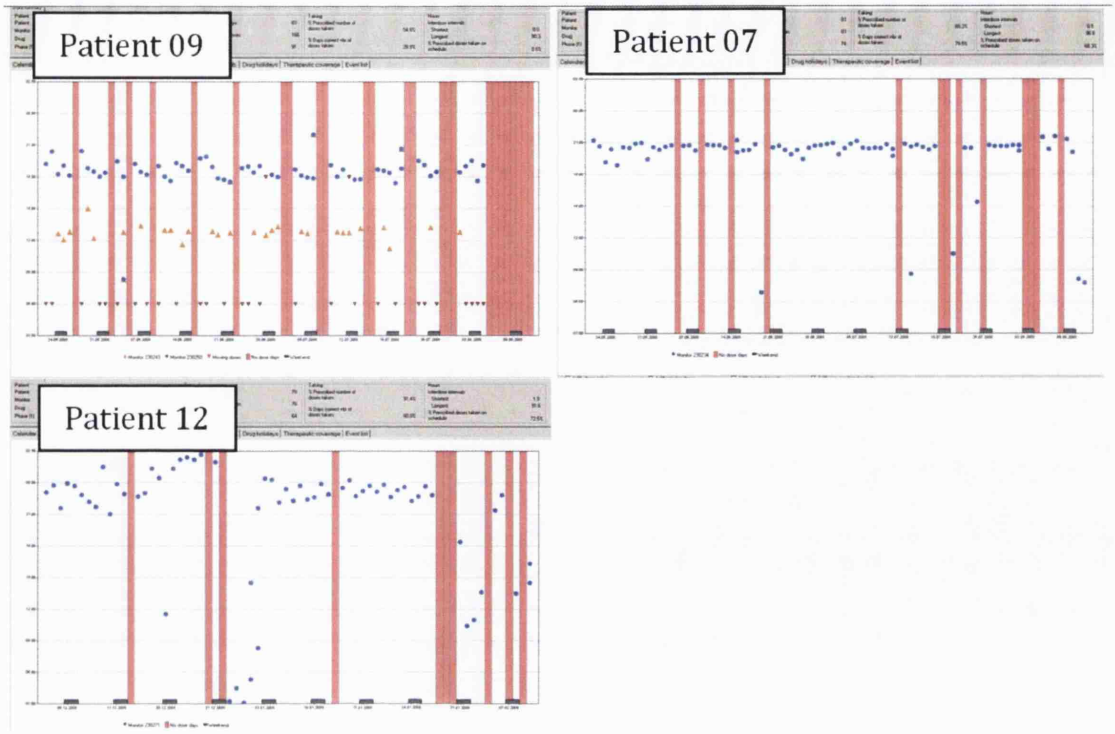

FIGURE 13 ADHERENCE PATTERNS: THE DECLINE OV ER TIME

2.4.6.5 THE GOOD-DECLINE-GOOD

The patients that were labelled 'good-decline-good' showed a pattern of good adherence immediately after starting the trial, then the adherence rate declined over a period of time, but then suddenly picked up about one week before the following hospital appointment (Figure 14). This may be an example of the 'Hawthorne effect', which describes the tendency for patients to improve their behaviour when they know they are being observed. Thus the effect lingers after having been enrolled in the trial, then the adherence rate declines somewhat and a week before the appointment the patients do not want to be 'caught out' by any of the clinical parameters and therefore improves adherence (the patients were aware that their drug blood levels were going to be measured after the trial).

Patient 20 is mainly intentionally nonadherent and estimates that he misses about 1/10 doses. Patient 18 says she generally does not miss doses, although she might very occasionally forget. The only exception was one week last year when she

missed all 7 doses because the pharmacy did not have any imatinib available to dispense. She says her mum calls every day to ask if she has taken her medicine and refers to using the Simpsons cartoon on TV as a clue for taking it and her young daughter often reminds her too. There are no specific clues that can explain the high level of nonadherence recorded by MEMS, except that she simply may not have wanted to disclose her level of nonadherence during the interview.

Patient 13 claims to never forget to take doses and to only miss on purpose, for example when she thought she was pregnant, a period which was not disclosed to the clinician overseeing her treatment. The last time this happened was not during the period of the trial (this was not asked specifically, but the patient told me the period she thought she was pregnant and this was not during the trial period). She later says that on the odd occasion she does forget she always take the dose in the morning, but there was only one recording of a dose taken earlier in the day. What is interesting is this patients' pattern of nonadherence as recorded by MEMS appears to be highly structured. She takes the imatinib perfectly for the first 8 days of the trial, followed by 8 days of taking a single dose (which appear to be the 100mg dose according to MEMS). After this there are 9 days of taking no doses, followed by 12 days of sporadic adherence/nonadherence. The subsequent 10 days she appears to have taken mainly the 400mg dose (according to MEMS monitor), and finally there are 9 days of perfect adherence (except one day of taking a single dose) before the following appointment. Considering that this patient says she is well read on the scientific literature related to CML treatment and imatinib, this might be an example of a patient who is adapting and managing her treatment as she sees fit. It seems as if she relies on the doctors to let her know if there are any adverse consequences:

> ...I kind of really trust my doctors in the hospital and it's very reassuring for me to come here every two months and see what my levels are like, if I am really honest I don't worry about it. Because my levels have never, over the last nine years, changed dramatically at all. They have always responded really well to Gleevec [imatinib]...//...I know the cells

have a chance again to divide and get more if I don't take it, but I know I can control it with Gleevec again, as soon as I start taking it... [Patient 13: lines 102-103]

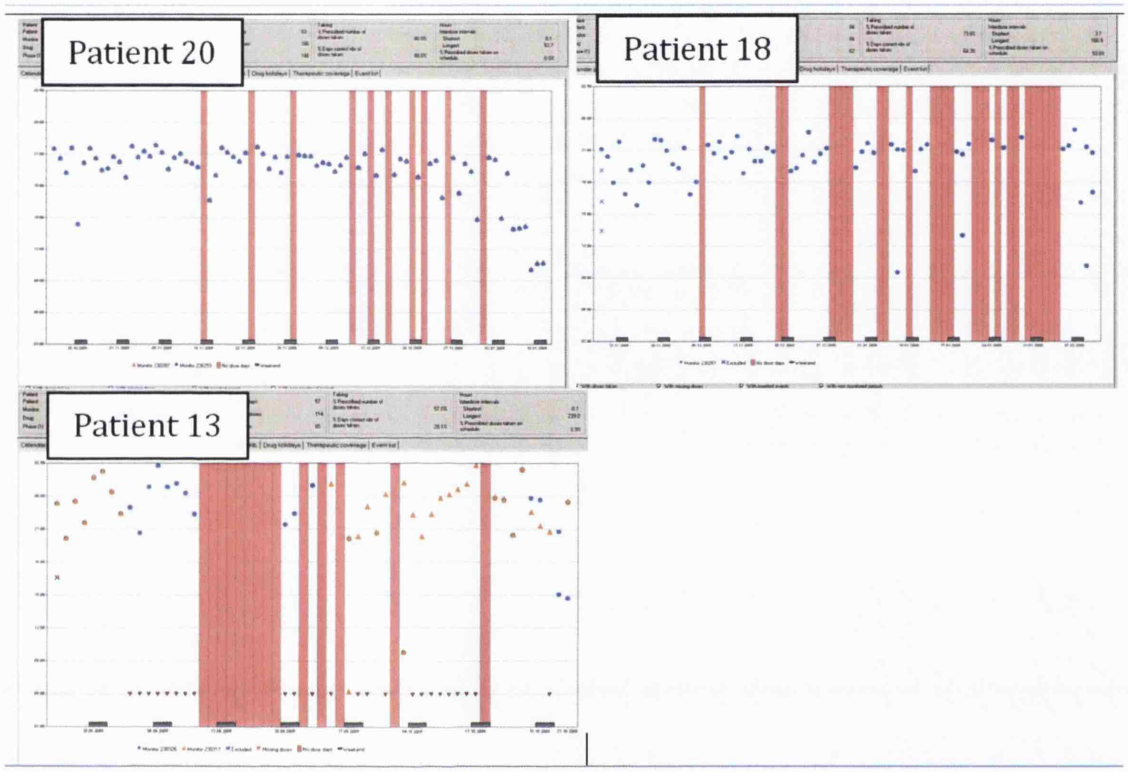

FIGURE 14 ADHERENCE PATTERNS: THE GOOD-DECLINE-GOOD

2.4.6.6 THE DOSETTE BOX USERS

The Dosette box users were patients who normally would use a Dosette box to reduce unintentional nonadherence (Figure 15). During the monitoring period, however, the patients were asked not to use their Dosette boxes. Patient 05 was seventy years old and had obviously used the Dosette box throughout the trial, although during the interview the person mentioned when probed that the Dosette had not been used during the trial. This highlights the difficulty of sometimes interpreting this type of pattern as very high levels of nonadherence.

In the case of Patient 10, it is less obvious that a Dosette has been used in periods during the trial and it would therefore be easier to interpret this as very high levels of nonadherence. Indeed, the blue crosses indicate openings that have been excluded by the person analysing the clinical trial (because multiple openings on a single day would cancel out missed doses on other days and the overall MEMS adherence rate would be inflated), and at times interpreted as the patent having not taken any doses on the days the MEMS was opened multiple times.

Nonetheless, when the patient was asked if he can remember any examples of times when it has been difficult to remember taking his tablets he tells the story of how during the trial it was very difficult as he could not use the Dosette box he would normally use to keep track of taking his tablets. After struggling for some days, he said he tried putting the tablets into his Dosette during two weeks, but as he thought the tablets faded slightly (normally he would just cut apart the plaster pack when filling the Dosette so that the tablets are not in contact with air) he decided it might be risky and instead kept the tablets in the MEMS. This made it very hard to keep track of tablets taken and he said he often had to open the bottle, count the tablets, calculate how many tablets should be there to figure out whether he had taken a tablet that day or not, and if he had not he would take a tablet. This story is perfectly illustrated by the chronology chart from the MEMS monitoring period and is a perfect example of the superiority of self-report and qualitative methods over other measurement methods in understanding patterns of nonadherence.

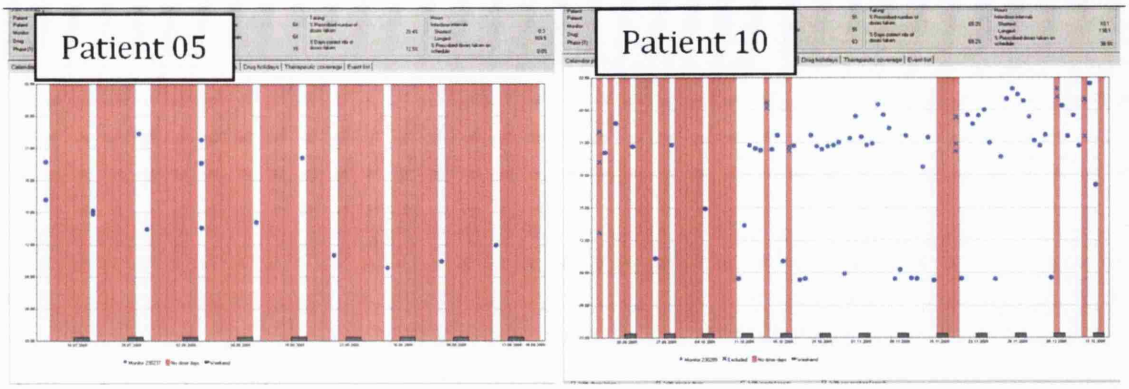

FIGURE 15 ADHERENCE PATTERNS: THE DOSETTE BOX USERS

2.4.7 PATIENT FEEDBACK SESSION: RESULTS AND REFLECTIONS

All the 87 patients who participated in the clinical trial were invited to attend the feedback session. Eleven patients attended the feedback session and all of them filled in the patient feedback form for the session. Of the 11 patients who attended the session, 2 were identified as nonadherent in the clinical trial with MEMS adherence rates <85%, and the other 9 had a MEMS adherence rate >90% during the clinical trial. In addition, 7 people who accompanied a patient to the session and 3 of the attending HCPs filled out the form. Furthermore, one patient, who was invited but could not make it to the session, wrote an email to the trial nurse with comments she said she would have raised had she been able to make the session. Extracts from this email are presented at the end of this section.

Even though only eleven patients managed to attend the session, many more patients expressed their interest and their regret that they could not attend. The two most common reasons patients mentioned for not being able to come were the extra travel it would take (many patients travel for hours to attend clinic at Hammersmith) and the extra time off work it would have entailed. However, several patients have asked for video recordings, transcripts or summaries of the feedback session and I am currently in the process of writing a summary that will be sent to all patients who participated in the trial.

It is possible that the patients who made it to the feedback session are somewhat different from the patients who did not attend. The views and opinions of these patients may therefore also differ and the feedback obtained in the session should be interpreted with caution.

The session turned out to be surprisingly interactive with great participation and discussion from the audience; at times strong emotions would surface. It was particularly interesting to see the way patients reacted and interacted with each other when it was revealed how many patients in the trial did not take their imatinib as prescribed.

The initial comments from the patients included that patients who were found to not take their imatinib should not be allowed to stay on the treatment, that they should be told the cost of the imatinib treatment and thus should be encouraged to adhere better by feeling guilty of wasting the money by not adhering (when someone else might not be able to afford it) and that clinicians should try and scare them by saying that if they do not take their imatinib as prescribed they will die "simple as that". The response to this included the angry question "What should you do if as soon as you swallow the imatinib you vomit?"; the reply was somewhat apologetic saying that of course he had himself been lucky enough to never have experienced any side effects, followed by a brief "yes, you are very lucky, aren't you?". A husband of a patient told us of his wife who would often become so nauseous when taking her imatinib she would not be able to take it maybe two days per week. He said the extra stress it would cause her to be told that she might die for missing these doses is not likely to help her.

This led on to a more positive discussion where patients shared experiences in ways to cope with side effects in general and nausea in particular, and the topic of "safe foods" was discussed, which also was mentioned in the patient interviews as described in section 2.4.3.1. "Safe foods" are what several patients refer to as food that when eaten together with the imatinib reduces or eliminates nausea and include anything from Kitkat chocolate bar to beans on toast and pasta

(carbohydrates might be the link?). Indeed research into "safe foods" was suggested by one patient as a new research area that might be helpful for CML patients taking imatinib.

The data from the feedback forms showed that all 21 responders strongly agreed (14) or agreed (7) that part 1 – measuring behaviour – was informative; all 21 strongly agreed (15) or agreed (6) that part 2 – feedback of trial results – was informative; and 20 strongly agreed (14) or agreed (6) that part 3 – feedback of interview results – was informative.

The feedback on the use of MEMS is presented in Figures 16 – 19. Figure 20 shows the feedback regarding whether the interview results gave a good picture of issues related to how the patients take their imatinib. It is clear that the people who attended the feedback session mainly had a positive attitude towards the use of MEMS monitoring, with most people believing the MEMS seemed useful for this type of trial, that they did not feel uneasy over the use of MEMS and that they thought researchers should use MEMS for similar trials in the future. The responses to the statement whether patients should have been told about the MEMS before starting the trial are a bit more varied, and because it is based on only 21 responses, it is difficult to draw any conclusions. All 11 patients agreed or strongly agreed that the interview results gave a good picture of issues they experienced with taking their imatinib (this question was meant to only be answered by patients, although some other people also opted to respond).

The further feedback/comments section included a statement from a person who had accompanied a patient to the session:

> "Now I know about MEMS – I will always look out for it and know I'm being observed. So it would probably not be such a good idea to tell us about the electronic caps!!"

Other comment from patients stated:

"Patients should be regularly told of the consequences of not taking [imatinib] as prescribed"

"Informative. Helpful. Reassuring – in terms of the side effects that I experience"

"Keep taking the pills!"

"Thank you for inviting us! Also thank you for all you do!"

The two points the patient who sent an email wanted to raise are written verbatim below. The points mirror the issues that have been expressed in the interviews, with the addition that promoting results from adherence trials to patients may reinforce the importance of taking medication.

- "As imatinib is taken every day and if you take it at the same time, it is very easy to forget if you have actually taken it. Suggest that like the contraceptive pill, tablet packaging is printed with the days of the week."
- "Taking tablets reminds you every day of the illness and, particularly at the beginning, makes you confront the situation. 'Forgetting' to take it removes this, until it becomes a routine activity and then the very routine nature means it can be hard to remember if you have taken it (see point raised above!). Promoting the finding of this study reinforces the importance of the medication in a positive way that helps address this."

A concluding remark about the feedback session is that it has had a lot of informal positive feedback from patients and health care providers around the hospital, where it was the first time a feedback session of trial results was organised for participants. This shows what great interest CML patients have in understanding research that is done in the name of their illness and treatment and highlights the importance of disseminating research data not just to related health care providers but also to the patients themselves.

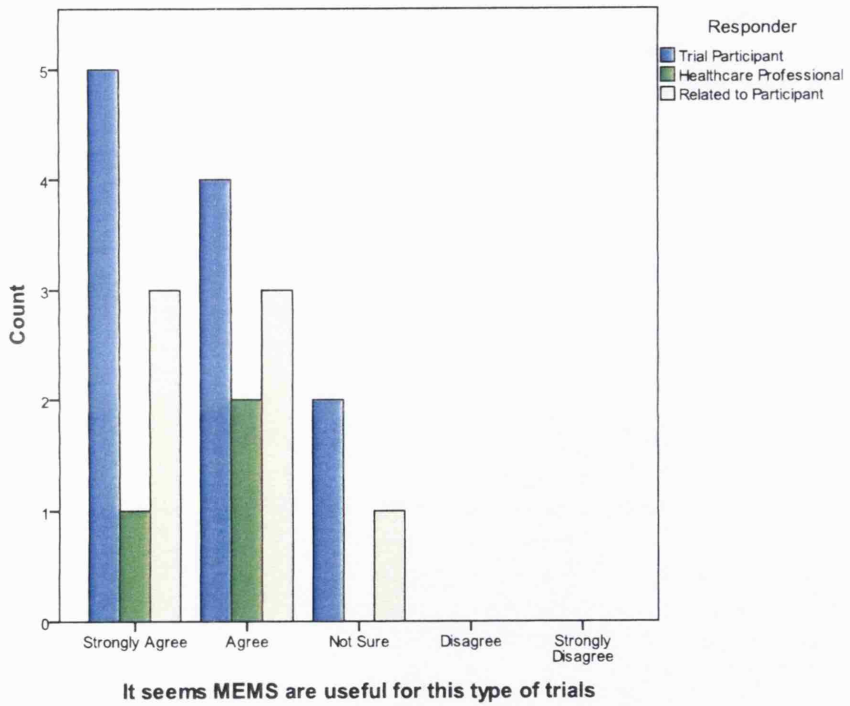

FIGURE 16 PATIENT FEEDBACK SESSION, COMMENTS AND FEEDBACK

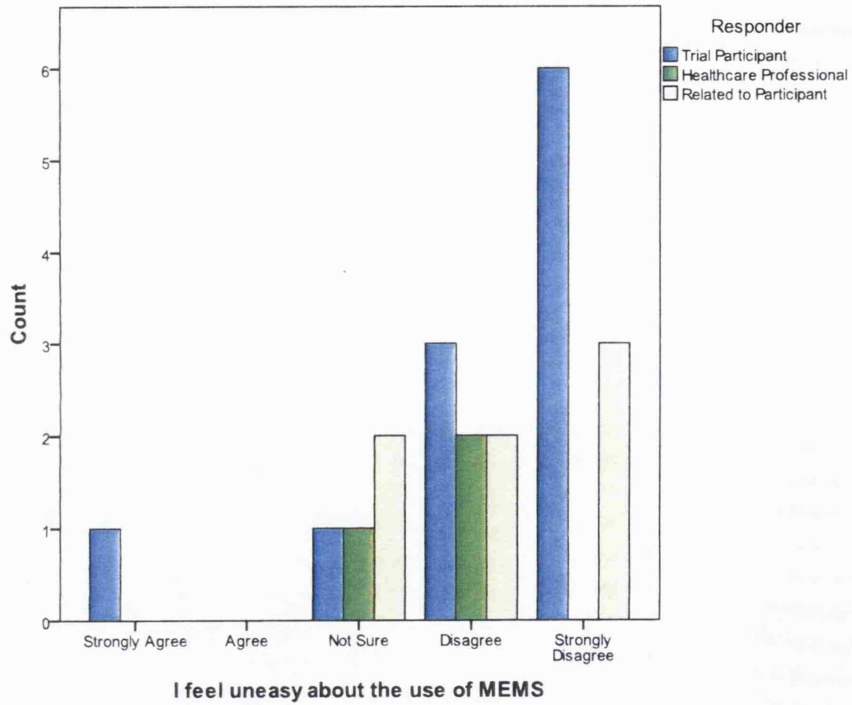

FIGURE 17 PATIENT FEEDBACK SESSION, COMMENTS AND FEEDBAC

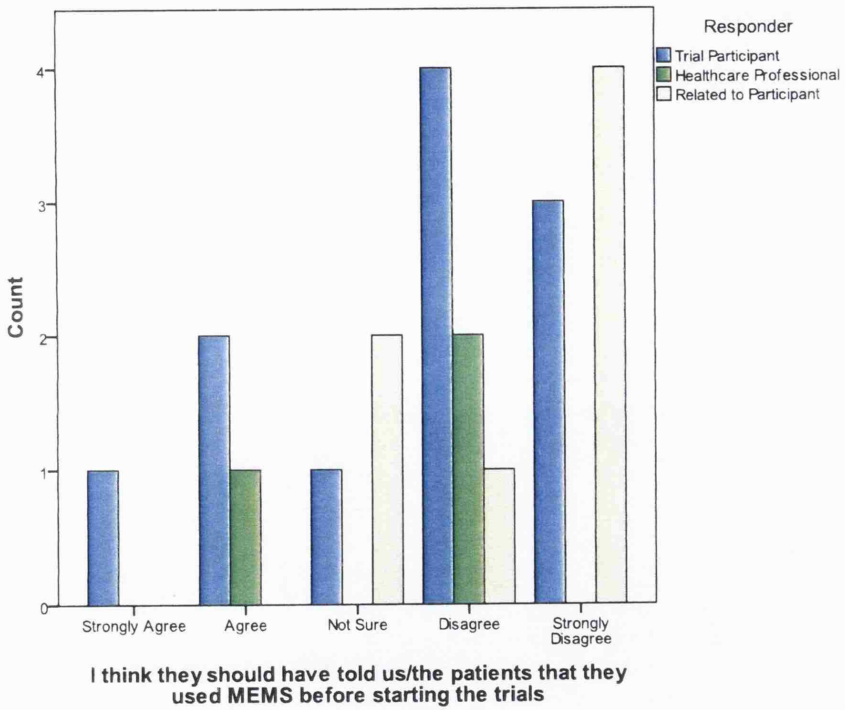

FIGURE 18 PATIENT FEEDBACK SESSION, COMMENTS AND FEEDBACK

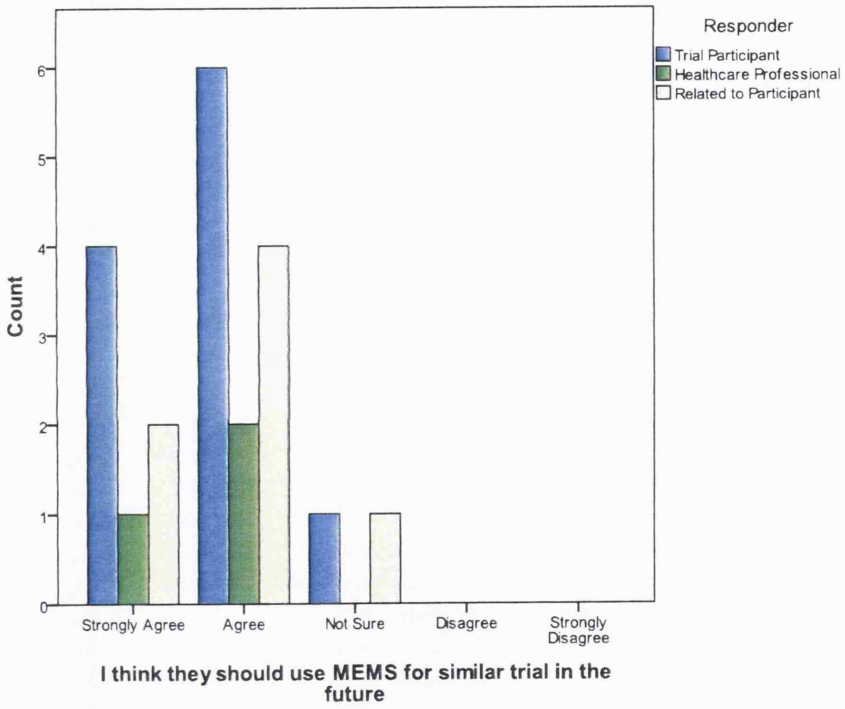

FIGURE 19 PATIENT FEEDBACK SESSION, COMMENTS AND FEEDBACK

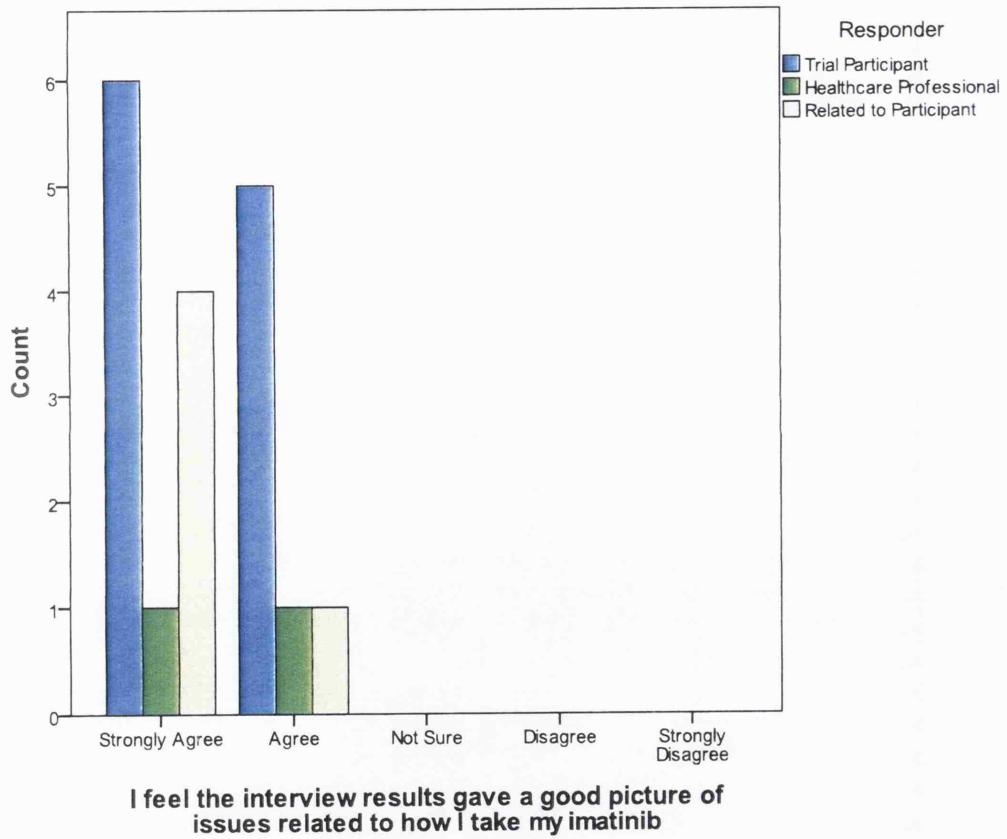

FIGURE 20 PATIENT FEEDBACK SESSION, COMMENTS AND FEEDBACK

2.5 DISCUSSION

In line with the existing adherence literature, CML patients expressed both intentional and unintentional reasons for their nonadherence to imatinib (WHO, 2003, Nunes et al., 2009). It was evident that the same patient could have both intentional and unintentional reasons to not adhere on different occasions. At times intentional and unintentional reasons overlapped or the one caused the other, such as when a patient first forgot to take the imatinib and upon remembering decides to skip the dose. That a patient reports both intentional and unintentional reasons for nonadherence is consistent with findings from other illness groups such as hypertension (Lowry et al., 2005, Lehane and McCarthy, 2007a), breast cancer (Atkins and Fallowfield, 2006), HIV (Wroe and Thomas, 2003) and general chronic illnesses treated in primary care (Clifford et al., 2008). The factors that seem to facilitate adherence was to fit the imatinib into the daily routine, using prompts to remember to take the tablets and finding ways of coping with side effects.

The most common reason for unintentional nonadherence was forgetfulness. This reflects the reasons for unintentional nonadherence in a range of other chronic illness groups (Clifford et al., 2008); indeed many studies use forgetfulness as the only operational definition of unintentional nonadherence (e.g. Wroe, 2002, Atkins and Fallowfield, 2006). However, recent reviews and guidelines do acknowledge other causes for nonadherence, such as access to medication and problems with dexterity (WHO, 2003, Horne et al., 2005, Nunes et al., 2009). This was also seen in the current interviews where a patient gave an example of the pharmacy not having imatinib available to fill the prescription and two other patients had problems swallowing the tablets. In addition, at times patients would become so nauseous after swallowing the imatinib tablets that they would immediately vomit the tablets back up; thus causing unintentional nonadherence, as the tablets could not be kept down. However, nausea was also one of the most common reasons for intentional nonadherence.

The most common reason given by patients in this sample for intentional nonadherence was to deal with side effects. This is in line with the literature on HIV medication, such as highly active antiretroviral treatments (HAART), which has to some (but more extreme) extent a similar side effect profile to that of imatinib including nausea, vomiting, fatigue, diarrhoea, skin rash and anaemia (Pound et al., 2005). However, imatinib is considered by health care providers to be generally well tolerated with most CML patients experiencing mild to moderate adverse effects (Moen et al., 2007). Imatinib also displays considerably less adverse effects than earlier treatments for CML and it is possible this is one reason why the potential impact of side effects on adherence seems to have been largely overlooked by health care providers working with CML patients.

Recently Noens et al. (2009) reinforced this idea as this study did not find a relationship between adherence and adverse events. However, the clinical trial from which this interview sample was taken found associations between a number of different side effects and low adherence rates (Marin et al., 2010), and in the interviews it was the most common reason given by patients for intentional nonadherence. Albeit, patients who were considered adherent with a MEMS adherence rate above 90% also expressed at times struggling with side effects and the difference between adherent and nonadherent patients may be the way that they coped with the side effects. The difference between the Belgian CML patients in Noens et al.'s (2009) study and the UK sample from the Marin et al. (2010) study, as well as the questions regarding coping with side effects that emerged from the interviews, calls for further large scale surveys of the reasons for not taking imatinib as prescribed in the wider CML population; in particular to sample more adherent patients that experience adverse effects of imatinib to see how they still achieve adherence.

Patients were also found to at times experiment with their treatment by reducing the dose or stopping the treatment for a period of time to reduce side effects or simply to see what happens with the leukaemia if imatinib was discontinued. Similar findings have been reported from a range of different illness groups such as

HIV, hypertension and asthma (Pound et al., 2005). This is consistent with the "common sense" paradigms of explaining adherence behaviour as captured by Leventhal's (1992) self-regulatory model of illness, which has also been partly operationalised through the necessity concerns framework (Horne et al., 1999, Clifford et al., 2008). According to these models patients' perception of their illness and treatment will influence how they take their medication and patients may thus alter (or "experiment with") their treatment accordingly.

Patients reported that the way they managed their treatment changes over time. There seemed to be a reduction in self-reported unintentional nonadherence over time and an increase in self-reported intentional nonadherence. In essence the patients expressed an initial high motivation to adhere to their imatinib caused by the shock of being diagnosed with CML. The reduction in unintentional nonadherence was exemplified by patients who said it was harder to remember to take their medication in the beginning before getting into the routine. However, there were patients who instead expressed a tendency to forgetting more imatinib doses as behaviour became automatic. Some patients reported seeking out adherence aids such as monitored dosing boxes and alarms to actively help reducing unintentional nonadherence due to forgetting.

In contrast, the increase in intentional nonadherence over time was expressed by several patients who said they were rigorous about taking their imatinib as prescribed in the early days of treatment. Subsequently, as the patients were given positive feedback from their clinician about their clinical response they tended to become more relaxed about taking the imatinib and thus reported increased intentional nonadherence. This would correspond to a reappraisal in perception of the illness and thus adaptation of the coping procedure (i.e. adhering to imatinib) according to Leventhal's (1992) model; in terms of the necessity concerns framework this could be explained as a decrease in the perceived necessity for adhering to imatinib as prescribed (Horne et al., 1999). There has been very little research reported on the way that nonadherence changes over time; although one study has shown that both intentional and unintentional nonadherence tends to

develop rapidly to newly prescribed medication in other chronic illnesses (Clifford et al., 2006).

In other cases patients' nonadherence seemed to have been more directly reinforced by the HCPs downplaying the impact that missing doses of imatinib can have on clinical response, whether due to patient nonadherence or due to planned treatment interruptions. In fact, several patients openly said they did not think missing 3-4 pills/month would affect their clinical response at all. However, three pills missed in a month are 10% of the total dose for these patients. As a consequence, the patients' chances of reaching complete molecular response has recently been shown to be reduced (Marin et al., 2010). This is particularly unfortunate as complete molecular response might for some patients constitute a cure, as patients have been able to discontinue treatment for CML at this stage without subsequent relapse (Rousselot et al., 2007, Mahon et al., 2002). It was also evident that many nonadherent patients relied on the laboratory parameters (eg BCR-ABL1 transcript levels as measured by PCR or blood counts) to detect adverse consequences of their nonadherence and relied on their clinician to let them know if this was the case.

This lack of understanding that even a few missed tablets could have a significant adverse effect on the outcome could be interpreted as a mismatch in communication between HCPs and CML patients. However, at the time of conducting the interviews there had not yet been any studies published that showed a relationship between nonadherence and reduced clinical response, as this was first shown by Noens et al. in 2009 and subsequently supported by our paper that was published in 2010 (Marin et al., 2010). The interview data suggest that HCPs tended to focus on positive feedback regarding clinical response; whilst 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). This dynamic may be influenced with the new evidence showing a link between adherence and response and clinicians may become more vigilant to potential adherence problems if patients are not responding as expected.

At the same time, very few patients said they had discussed nonadherence with the HCPs involved in their care. As discussed in the introduction, it has been argued that patient–provider communication is the single most important factor mediating health care provider's effect on adherence (Alexander et al., 2006). This implies it may be beneficial to encourage HCPs to initiate open and non-judgemental discussions regarding adherence and likely consequences of nonadherence with the patients, as well as being honest about risks of treatment interruptions. To achieve this, it is important to relay data in a manner that all patients can understand. For example, instead of saying "it does not matter if you miss the odd dose", which is open to interpretation; it might be better to say "if you miss more than two doses in a month your chances of maintaining a good response is reduced".

However, improving communication should not be done solely with the aim of increasing adherence per se, but also to increase patient autonomy and encourage patient involvement in making decisions about their treatment (Nunes et al., 2009). All patients have a right to not adhere if they do not want to or to alter treatment to better suit their life (although this right could be challenged when considering highly infectious diseases such as tuberculosis). However, it should be the HCPs' responsibility to make sure that the patient has been given and has *understood* the relevant information to be able to make an informed decision about their treatment. In addition, different patients may want to have different levels of involvement in making decisions about their treatment. For example, research has shown that patients of younger age and of higher social class may prefer a greater involvement in treatment decisions than others (Garfield et al., 2007). Patients should therefore be allowed to defer treatment decisions to the health care provider if desired.

Nonetheless, referring to imatinib as having largely transformed CML from being a terminal to a chronic illness that can be managed by the patients at home should not make us forget that CML is inexorably fatal if left untreated and the chances of achieving a good response is significantly reduced if the patient is nonadherent

(Noens et al., 2009, Marin et al., 2010). Indeed, not all patients respond to therapy and some patients are diagnosed when the illness is already at an accelerated or blast phase, severely reducing the long term prognosis of the illness (Moen et al., 2007). Therefore, the levels of patient autonomy to "self-regulate" their treatments that has been put forward in respect to other chronic medication may not be appropriate in more immediately life threatening illnesses such as CML (Pound et al., 2005).

The analysis of the different patterns of adherence was done by summarising MEMS data from the trial monitoring period and comparing these to the patients' narratives about adherence/nonadherence. The analysis revealed 6 distinct patterns of adherence, which gave insight into patients' behaviours as well as provoking thought regarding the best way to access and measure patients' adherence behaviours. The patterns of the 4 adherent patients appeared consistent with timings and dosing schedules followed; in one case there were a few missed doses recorded, but it seemed highly likely that the patient had taken out extra doses that covered the days missed indicating that doses had been ingested every day.

The nonadherent patterns seemed to fall into 5 distinct groups. The occasional and the frequent "random" nonadherers were the patients who had missed doses, but there seemed to be no particular pattern to explain the missed doses. Of the 9 patients who either occasionally or frequently missed doses, most experienced both intentional and unintentional nonadherence and only 2 patients said they were not nonadherent (1 occasional and 1 frequent). In both these cases the patients referred to always keeping imatinib tablets on them when going out. It is not possible to say whether the missed doses recorded can be explained by the patients taking imatinib from second sources, it might explain some missed doses but not all. It does, however, raise questions regarding how far we can understand MEMS results without having qualitative information to aid the interpretation.

The adherence patterns of the patients who showed a decline in adherence rates over the monitoring period seemed to have been affected by the enrolment into the trial. This is similar to the patient patterns with good adherence rates in the beginning and at the end of the monitoring period with a distinct decline in adherence rate in the middle. The effect of the start and end of trial appointments are apparent, but it is not possible to say whether these patterns are similar to adherence patterns during normal care or not. It could be that a decline in adherence rate over time is an example of the so called "Hawthorne effect", which is that people tend to behave better when they know they are being observed. However, this effect tends to reduce with time if observations are ongoing. On the other hand, where the adherence rates are good at the start and at the end of the trial, but lower in the middle, it may rather be examples of so called "white coat adherence", which is that patients tend to adhere better around the time of clinical appointments. Although there may have been an influence of the trial methods on the adherence rate in these patients, the monitoring has still fulfilled the aim of measuring the actual adherence behaviour that these patients have engaged in during this period.

Finally, there were two examples of the distinct patterns that can arise when trying to use MEMS to measure adherence behaviour of patients that during normal care use Dosette boxes. In one case the patient had obviously just continued using the Dosette box during the trial. In the other case, however, the trial methods had caused much difficulty for the patient. This most likely resulted in an increased number of missed doses. In addition, because the patient had used the Dosette box for a shorter period during the trial it was not apparent from the MEMS readings that the patient had used a Dosette box. It simply appeared as if the patient had a very high rate of nonadherence.

2.5.1 LIMITATIONS

This is a qualitative study, which is interpretative, in a small sample of CML patients treated at a 'centre of excellence' specialist hospital in the UK. The results

can therefore not necessarily be generalised to other CML patient populations from other hospitals, or in other countries. The sample included only patients that had been treated with imatinib for 2 years or more, and it would have been interesting to explore adherence in newly diagnosed patients, and patients who have used imatinib for less than 2 years.

2.5.2 FUTURE RESEARCH

The results from these interviews have furthered our understanding of the reasons why some CML patients do not adhere to imatinib as prescribed, including intentionally missing doses to deal with side effects and unintentionally forgetting. The results have also highlighted that some feedback from health care providers may reinforce nonadherent behaviour by reducing the patients concerns for the consequences of missing doses. These results lay the ground work for further research into CML patients' adherence to imatinib and the factors affecting nonadherence. However, quantitative studies are also needed to test the generalisability of the adherence, nonadherence and medication management themes experienced by this sample to other CML populations.

Future research should also include testing the theories available to explain patient medication taking behaviours, such as the Accident Causation Framework {ACF; Reason 1990}, and evaluate their ability to explain nonadherence in cancer patient prescribed oral anticancer drugs. In addition to further our understanding of nonadherence to oral anticancer treatments per se, finding appropriate theory to explain nonadherence is also the first step towards developing interventions to facilitate optimal adherence to these drugs. It is important that intervention development is theory driven to allow development of robust randomised controlled studies, so that the active components can be identified and effectiveness can be evaluated, as advocated by the medical research council in their framework for developing complex interventions to improve health (Craig et al., 2008, Campbell et al., 2000). The ACF usefulness in explaining CML patients'

reasons for nonadherence, which were identified in these interviews, will be analysed in-depth in the following chapter 3 of this thesis.

Finally, to support future research and intervention development, as well as clinical practice, there is a need to develop appropriate measurements of adherence to oral anticancer drugs. This is an issue that will be discussed further in chapter 4 of this thesis.

2.5.3 CONCLUSIONS

Clinical trial results show that a quarter of CML patients that have been treated with imatinib for a minimum of 2 years are taking less than 90% of their prescribed doses of imatinib (Marin et al., 2010). The reasons CML patients expressed for not taking the imatinib can broadly be dichotomised into intentional and unintentional reasons. Unfortunately, taking less than 90% of imatinib doses significantly reduces the chance of obtaining and sustaining the treatment goal of complete molecular response, in which no further leukaemic cells can be detected in the bone marrow (Marin et al., 2010). However, many patients are unaware how important it is to adhere to imatinib as prescribed, and assume that missing 'the odd dose' is not going to affect their response. Nevertheless, most patients try to adhere to the best of their ability, and they use a range of strategies to cope with side-effects and to fit imatinib treatment into their daily lives.

There were a range of different patterns of adherence recorded by the MEMS, which has given insight into the patients' medication taking routines. In addition, the analysis of patterns revealed some potential difficulties in judging complex medication taking behaviour based on MEMS and has highlighted the potential advantages of simply asking the patient to self-report on their adherence behaviours. The knowledge gained from these interviews form a basis on which to build future research and adherence interventions to support patients with CML, and other cancers that can be treated with self-administered drugs, to adhere optimally to their oral anticancer treatments.

CHAPTER 3: EXPLAINING PATIENTS' REASONS FOR NONADHERENCE USING THE ACCIDENT CAUSATION FRAMEWORK

3.1 INTRODUCTION

The aim of this thesis was to advance our understanding of patients' nonadherent behaviours, as well as the related theory and measurements, by taking a system wide perspective. The focus of this chapter is the advancement of theory.

The introductory chapter identified limitations in the social cognition theories (SCTs) that are commonly used to explain nonadherence. The main limitations are that the SCTs can only explain intentional nonadherence, although a large proportion of nonadherence is unintentional {Nunes, 2009; Horne, 2005; WHO, 2003). In addition, as the name for this group of theories implies, these theories can only account for the influence patients' cognitions has on adherence. Other factors that may influence adherence to medication, such as access to medication, medication formulations, forgetfulness and prescribing errors are left unexplained. These factors have been associated with nonadherence in the adherence literature at large {Nunes, 2009; Horne, 2005; WHO, 2003), as well as in the specific case of chronic myeloid leukaemia patients' adherence to imatinib, as presented in chapter 2.

The introduction presented three theories that may account for both intentional and unintentional nonadherence, namely the utility theory {Wroe, 2002; Wroe, 2003; Lehane, 2007}, the perceptions and practicalities approach (Horne et al.) and the Accident Causation Framework (ACF; Reason 1990). Having reviewed the evidence for using any one of these three theories to advance our understanding of intentional and unintentional nonadherence, as well as the system influence on nonadherence, it was concluded that the ACF seemed the best suited. Consequently, this chapter will investigate how we may further our understanding of patients' reasons for nonadherence by taking the perspective that nonadherence can be seen as a medication error that may be explained by the ACF.

3.1.1 NONADHERENCE AS A MEDICATION ERROR

When taking the system perspective of understanding nonadherence as a medication error we are not only taking advantage of knowledge from a related disciplines that may further our understanding of the causes of nonadherence, but we are also moving away from holding the patients solely responsible for their nonadherence. The traditional person centred view focuses on the person that 'fails' to adhere correctly, argues for individual responsibility / blame and states that solutions should focus on changing the person's behaviour for the better.

The system approach promotes that all people are fallible and that nonadherence is to be expected by most people at some point. Research is focused on understanding all the factors that influence nonadherence, including personal and system related factors, and solutions are generally aimed at improving the whole system.

The two concepts of medication error and nonadherence are similar: if a treatment is not administered correctly by a health care provider it is referred to as a medical error; if a treatment is not (self-) administered correctly by a patient it is referred to as nonadherence. However, nonadherence to medication has previously rarely been referred to as a medication error (Barber, 2002); although exceptions exist.

For example, Hulka et al (Hulka et al., 1976), included 357 patients with diabetes mellitus or congestive heart failure, as well as the 46 physicians treating these patients, in a study of adherence (the study used the term compliance). Data was collected from each patient / physician pair; physicians reported on drugs prescribed (also verified by medical records and pharmacy records) and verbal treatment schedule recommendations given to patients; patients reported on drugs prescribed, treatment schedule understood, as well as the level of adherence to prescribed treatment and adherence to the treatment schedule. The analysis included only prescription drugs that had been dispensed by the pharmacy and not over the counter drugs. Using this information they concluded that there were four distinct 'medication errors' in these patients groups (average error rate%):

- Omission error = drugs the patient was not taking of those prescribed (19%)
- Commission error = drugs taken by patient that were not prescribed (19%)
- Scheduling misconception = prescribed drugs taken incorrectly where the correct schedule was not known to the patient (17%)
- Scheduling non-compliance = prescribed drugs taken for which the patient knew the correct schedule but did not take as prescribed (3%).

In this study, there was no information on whether omission and commission errors were done unintentionally or intentionally by the patients, although scheduling misconception is per definition unintentional and scheduling non-compliance is per definition intentional (Hulka et al., 1976). The general argument of the paper, however, is that what may be considered 'noncompliance' by the patient (implying intention), may in fact be based in the patient's misunderstanding of the prescribed treatment regimen and should thus be considered 'errors'.

This is consistent with an argument put forward in a book chapter by Leon Gordis, published in the book 'Compliance in Health Care' (Eds Haynes, Taylor & Sacket, 1979), which is highly cited in the research field of treatment adherence:

> "It is important to distinguish between noncompliance and medication errors. In the case of medication errors, the patient's intellectual limitations, or other circumstances may have confused him so that he does not or cannot follow the instructions. On the other hand, noncompliance implies intent to not follow instructions" Gordis (1979; p25)

This argument probably reflects the divergence (or emergence) of the research fields of medical errors and nonadherence. In addition, it is noteworthy that the definition Gordis (1979) used above for medication errors closely resembles definitions of unintentional nonadherence. Therefore, this statement probably also reflects the subsequent decades focus of adherence theorists on explaining intentional nonadherence only.

There is evidently a close, and occasionally overlapping, relationship between nonadherence and medication errors, which is also reflected in discussions of the patients' general intent to take prescribed medication and the allocation of responsibility for making sure the patient take their medication as prescribed. This close relationship has prompted a natural merging of the two areas in certain fields, perhaps most notably in the field of adherence to oral anticancer treatments.

The merging of the concept areas of error and adherence is, for example, reflected in the shift of the language used when discussing patients prescribed highly toxic oral anticancer treatments; such as referring to the patient as "administering" these drugs (BOPA, 2004), instead of being "adhering to" or "compliant with"; hence nonadherence have been referred to as an administration error. This natural shift may initially have arisen due to the severe consequences over dosing of these drugs can have, including death (Birner et al., 2006).

There is also a natural shift when discussing oral anticancer drugs of solely holding the patients responsible for adhering as prescribed, or self-administering as directed, to focus on the wider system surrounding the patient. For example, a position statement on care of patients receiving oral anticancer drugs, including imatinib, issued by the British Oncology Pharmacy Association states:

> "Responsibility for administration of oral drugs ultimately lies with the patients (or a relative or carer) but it is the responsibility of all members of the multidisciplinary oncology or haematology team to ensure, as far as practically possible, they are adequately prepared for this" (BOPA 2004, pp. 422).

There are a number of safety issues that have been raised in relation to the increased use of oral anticancer treatments; in particular safety issues related to health care providers (HCPs) prescribing and monitoring these drugs and safety issues related to the patients' self-administration of these drugs. A study on safety issues relating to oral anticancer regimens reported instances of over administration and referred to these instances as medication errors (Birner et al., 2006). The case studies that Birner et al. (2006) referred to were examples of over dosing due to patients having misunderstood the treatment regimen, which

included periods where no medication should have been taken but the patients had continued use throughout the whole period.

A rapid response report by the National Patient Safety Agency (NPSA, 2008) reported on 445 incidents that involved oral anticancer treatments (including imatinib) and stated that 22% of these were administration errors, presumably mostly erroneous self-administration which would be synonymous with definitions of nonadherence. This shift towards referring to nonadherence to oral anticancer drugs as errors due to the safety issues surrounding patient self-administration of oral anticancer drugs implies that theory derived from the human error and safety research fields may also be useful to understand nonadherence to oral anticancer medication, as well as nonadherence to other self-administered medications.

Nonetheless, the overlap between the research fields of medication errors and medication adherence has mainly been implicit, and the suggestion of using the human error paradigm to understand both intentional and unintentional causes of nonadherence was first put forward explicitly by Barber in 2002. The paper explored the similarities between the concepts of medication errors and nonadherence in relation to safe use of medicines, and argues that nonadherence can be conceptualised as a medication error; an argument that has been strengthened by recent literature (Barber et al., 2005, Garfield et al., 2009).

3.1.2 THE ACCIDENT CAUSATION FRAMEWORK

Barber (2002) suggested the possibility of using the ACF (Reason, 1990; Reason, 1993; Reason, 2000; Reason, 2001; Reason, 2008) to explain nonadherence; the theory that is most widely used in the field of medication errors and safety research.

Reason's ACF (1990) is closely related to Rasmussen's skill-rule-knowledge framework (1983). The skill-rule-knowledge framework is primarily directed to explain serious errors made by people in supervisory positions in industries, such as nuclear power plants and aviation, which can have disastrous consequences. The framework explains the cognitive processes underlying task performance and

the skill-rule-knowledge levels correspond to human performance on tasks with decreasing familiarity, as well as the different errors that can arise at these levels. Rasmussen (1983) also introduced the idea that human errors are not primarily caused by spontaneous human variability in task performance, but that events within the system act as precursors that make errors more likely to occur (Rasmussen, 1983).

Reason's ACF operationalises the skill-rule-knowledge distinctions of errors and places these within the system context by explaining how environmental conditions that trigger errors are created by latent conditions such as management decisions and organisational processes (Figure 21, pp. 170). According to this framework, the cognitive functions that underlie human performance can explain the different ways in which actions fail to reach the desired outcome, either intentionally or unintentionally (Reason, 2008, Reason, 2000, Reason, 1990, Reason, 2001, Reason, 1993). Intentional actions include violations, where the actor knows the right process but chooses not to follow it and mistakes where the actor does not know the correct process and instead uses mistaken rules or knowledge that leads to failure in reaching the desired outcome. Unintentional slips and lapses are caused by failures of attention and memory. However, definitions of the above mentioned concepts have changed somewhat over time and the implications of this will be discussed in the following section.

3.1.3 DECIDING ON DEFINITIONS: INITIAL CHALLENGES WITH THE ACCIDENT CAUSATION FRAMEWORK

There are some major challenges with working closely with Reason's theory in that concept definitions have changed over time and supporting arguments are at times vague. This is most likely a reflection of Reason's own reassessment of previous writings and a common occurrence in relation to theory development, but for people new to the field it can be a challenge; in particular as later definitions appear less clear than early ones.

For example, the early writings of Reason made a clear distinction between slips and lapses (e.g. 1990; 1993; 2001). Slips were said to be caused by failure in attention and tended to be observable, whilst lapses were said to be caused by

failure in memory and tended to be internal. However, by the publication of The Human Contribution in 2008 slips and lapses are not assigned specific definitions (Reason, 2008). In fact only slips, but not lapses, are listed in the index of the book. The reason for this seems to be that it is difficult to reliably and validly distinguish whether a slip or a lapse was caused by a failure in memory or attention, and because attention and memory are interlinked. For example, if attention is not directed towards some information to be remembered, it is likely to be forgotten. Therefore, it was decided that, for this study, slips and lapses would be grouped together for the adapted framework that is put forward to explain nonadherence.

The definitions of violations have also developed over the years and may now be considered 'over defined'. For example, initially violations were divided into routine, exceptional and sabotage (1990); by 1993 optimising violations were added to the list. In a paper published 2001 it was argued violations fall into 3 main groups and sabotage had thus been dropped. In a book from 2008 the four main groups of violations (routine, exceptional, optimising, sabotage) were again put forward. However, the 4 categories have now got an extra dimension of skill based violations (routine and optimising violations), rule based violations (situational violations) and knowledge based violations (exceptional violations). This extra layer of classification has made it very hard to distinguish between the different constructs. For example, it is argued that skill based violations are likely to be less deliberate than rule based violations; although all violations are supposedly deliberate.

There is also difficulty differentiating between mistakes and violations. For example, it is possible to distinguish between rule based mistakes and rule based violations by verifying whether the actor knew the correct process or not. However, it is very difficult to distinguish between knowledge based mistakes and knowledge based violations. The explanation put forward by Reason states:

> "just as mistakes are intentional actions carried out in the belief that they will achieve their desired end, so situational violations are deliberate acts carried out in the belief that they will not result in bad consequences" (Reason, 2008, pp. 54)

Therefore, it was decided that this study would retain the original definitions and classification of violations from Reason 1990, 1993 and 2001. The original ACF (Reason 1990; 2001) is displayed in Figure 21 below.

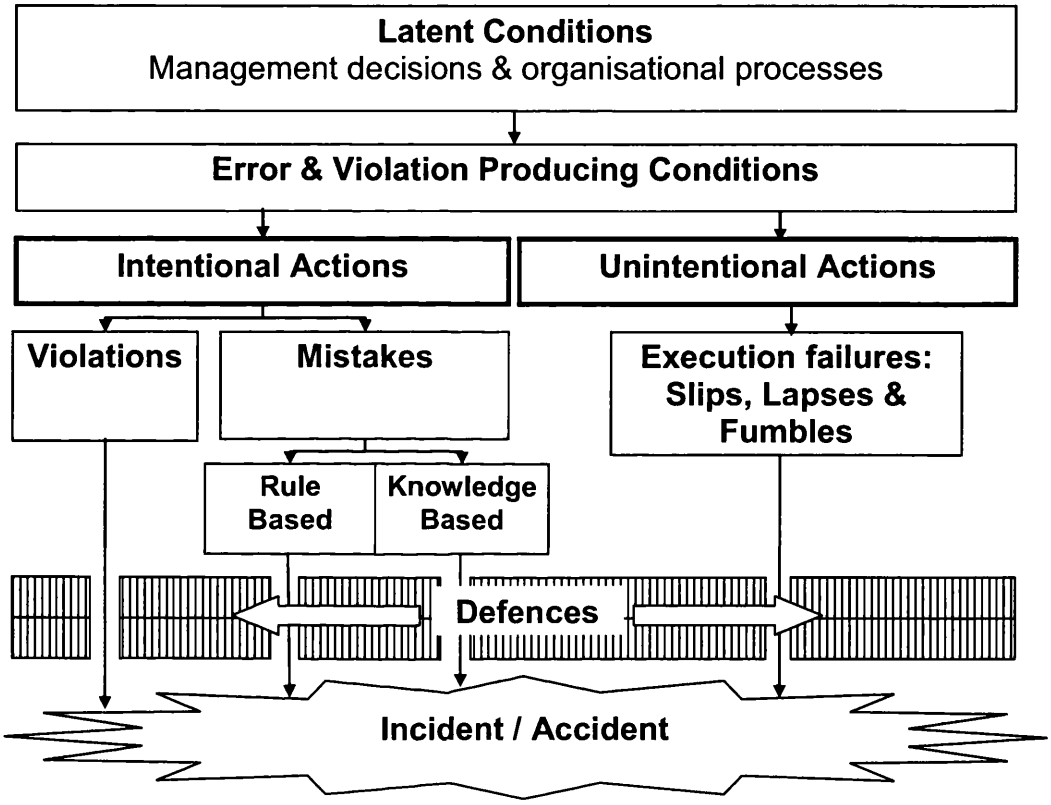

FIGURE 21 THE ACCIDENT CAUSATION FRAMEWORK, ADAPTED FROM REASON 1990; 2001

3.1.4 APPLYING THE ACCIDENT CAUSATION FRAMEWORK TO NONADHERENCE

Similar to the intentional and unintentional actions in the ACF, nonadherence behaviours can be subdivided into intentional and unintentional actions (WHO, 2003, Nunes et al., 2009). In addition, similar to human errors in general, nonadherence is a behavioural response that is guided by mental processes and cognitions, which may be considered inadequate or erroneous. However, further development work is needed to adapt the ACF appropriately to nonadherence on both conceptual and methodological levels before it can be operationalised

(Barber, 2002). In addition, ethically charged issues of allocating blame and responsibility, value-laden terminology and patients' rights to not adhere would need to be addressed.

Reason's framework as it may be adapted to nonadherence is displayed in Figure 22 (pp. 173). In Barber's (2002) paper the ACF (Reason, 1990) was introduced as a taxonomy of nonadherence, classifying patient's nonadherence behaviour according to intentional violations and mistakes, and unintentional slips and lapses. This is intuitive and has been shown to be a useful approach to classify intentional and unintentional nonadherence, as well as explain the causes of unintentional nonadherence (Barber et al., 2005).

Barber, Safdar and Franklin (2005) presented an exploratory study that supported the use of Reason's behavioural framework to explain nonadherent behaviours. The study interviewed 87 patients and asked them to recall episodes of nonadherence, which was analysed according to Reason's ACF. The results showed that Reason's framework was useful in explaining unintentional nonadherence, such as forgetting tablets. However, the framework was less useful in explaining intentional nonadherence (Barber et al., 2005). This was in part because it is not as straight forward to determine what the right and wrong processes are in relation to patients' adherence to medication as it is to determine what the right and wrong processes are in industrial settings.

The difficulty is mainly due to the different perspectives on what might constitute the 'right way to adhere to treatment' between the patient and the HCPs. For example, patients may experience unacceptable levels of adverse effects and therefore decide that the right course of action is to stop taking the medication. HCPs, on the other hand, may consider the adverse effects to be acceptable (compared to alternative treatments or to the health implications of discontinuing the treatment) and therefore think 'the right course of action' is for the patient to continue taking the treatment. Therefore, the authors called for further research into developing the ACF within the field of adherence research (Barber et al., 2005).

The first step in adapting the framework, with the prospect of later operationalising the framework in full to explain nonadherent behaviours, is to define the concepts within the framework in accordance with nonadherence (Table 6, pp. 176). I am suggesting that nonadherence should be seen as the 'action' performed by the patient and that 'the incident/accident' is reduced clinical benefit.

By defining the 'incident/accident' as reduced clinical benefit it is possible to better decide what is the 'right' behaviour. In relation to CML patients on imatinib specifically, it was clear from the interviews (presented in Chapter 2) that patients did want to manage their CML and obtain a good level of clinical response, and that they relied on the drug (imatinib) to do this. Similarly, it can be presumed that patients in general who are experiencing serious or life threatening illnesses would prefer to obtain as good a clinical response as possible. In line with this argument, it is possible to determine that any actions that will reduce the clinical benefit of the treatment can be considered 'incorrect', hence defined as an 'error' or 'nonadherence', from both the patients' and the HCPs' perspectives.

There are obviously still issues when considering a patient who is experiencing unacceptable adverse effects from the drug and therefore stop taking it. In the cases where the prescribing clinician agrees that the level of side effects are unacceptable, good clinical practice would be to stop the drug. However, when the patient and the clinicians do not agree, or indeed when there has not been any communication regarding side effects, and the patients stop taking the drug unbeknown to the clinician the patient would still be classified as nonadherent. The key to classifying this behaviour thus depends on the communication and agreement about missing doses between the clinician and the patient.

The taxonomy of nonadherence once it has occurred would be the same as when classifying errors, according to mistakes, violations and slips and lapses. The system factors of 'latent conditions' and 'error and violation producing conditions' also translates directly to the health care system factors that may influence nonadherence to treatment.

Defences is another group of concepts that was not discussed in the previous two papers that proposed using the ACF to explain nonadherence (Barber, 2002, Barber et al., 2005). In the original framework (Figure 21, pp. 170) defences is what protects the errors from translating into an accident or incident. However, there are some problems with adopting this exact approach when using the framework to explain nonadherence.

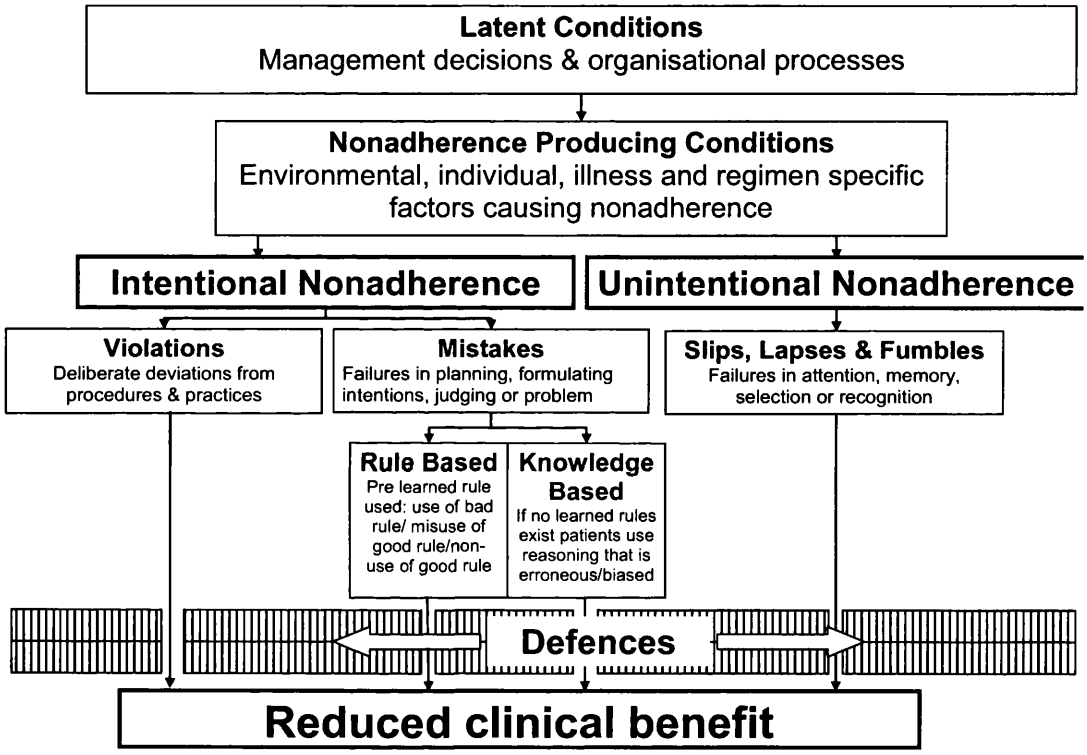

FIGURE 22 REASON'S ACCIDENT CAUSATION FRAMEWORK FROM REASON 1990; 2001, ADAPTED TO NONADHERENCE

The problem arises when considering what may constitute defences in terms of nonadherence. One of the first things that spring to mind is likely to be interventions to reduce nonadherence. However, if the defences, as situated in the ACF, is adapted directly to nonadherence, defences is in fact not situated between the causes of nonadherence (nonadherence producing conditions) and the actual nonadherence, but between the nonadherence and 'reduced clinical benefit'. This seems inappropriate as in relation to adherence to imatinib, for example, there are no other 'defences' for reduced clinical benefit than to adhere to the treatment.

Therefore, defences may be better situated before nonadherent behaviours as interventions taken to reduce the occurrence of nonadherence. In line with this argument, Figure 23 below includes this adaption, which is the framework that was the theoretical basis for this study and that was used in the analysis (this framework was later readapted after analysis, including where defences are best situated and the addition of a possible feedback loop within the system, which will be presented in the discussion section).

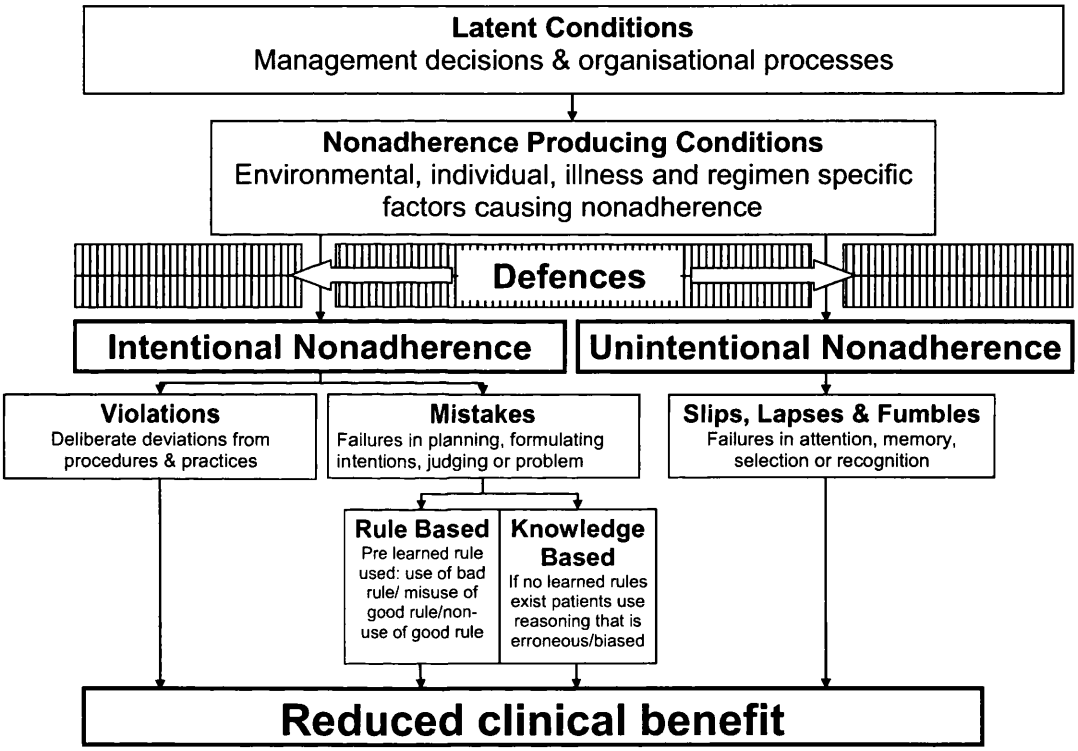

FIGURE 23 THE ACCIDENT CAUSATION FRAMEWORK ADAPTED FROM REASON 1990; 2001, AS USED FOR ANALYSIS OF INTERVIEW DATA

In summary, using Reason's ACF (1990) to investigate nonadherence widens the focus from a spotlight on individual patients' internal processes – as promoted by the SCTs discussed in the introduction – to encompass the whole system that may influence patients' nonadherence. The responsibility for taking medication as prescribed is thus no longer solely dependent on the patient, but includes external factors such as communication between the patient and the health care provider, the environment and the health care organisation that may influence patient behaviour. This chapter will explore the use of the ACF to explain patients' reasons

for nonadherence and the aims and objectives for doing this are set out in the following section.

3.2 AIM

The aim of this study is to explore the usefulness of Reason's Accident Causation Framework (Reason, 1990) in explaining nonadherence to prescribed medication. To reach this aim the following objectives were set up:

1. To explore the applicability of the accident caution framework to explain nonadherence to imatinib in CML patients.
2. To develop the ACF to better explain nonadherence to medication.
3. To adapt terminology and definitions to be better suited to the field of medication adherence.

3.3 METHODS

The analysis reported here is a post-hoc analysis of the interview data presented in chapter 2.

3.3.1 PARTICIPANTS AND CONSENT

The qualitative study was approved by Lewisham NHS medical research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

The data used in this *post-hoc* analysis is the same interview data used in the constant comparison analysis presented in chapter 2. Therefore, please refer to Chapter 2, section 2.3.3 (pp. 98), for full details of participating patients, consent procedures, recruitment and confidentiality. In total 21 chronic myeloid leukaemia (CML) patients prescribed imatinib were interviewed. Seventeen were considered to be nonadherent by taking ≤90% of their prescribed imatinib and 4 were considered adherent by taking >90% of their prescribed imatinib, according to medication events monitoring systems (MEMS). For further details related to

MEMS and the adherence rates of patients included in this sample, please refer to chapter 2 section 2.1 (pp. 90).

3.3.2 DEFINITIONS

Table 6 displays the definitions of the constructs of Reason's ACF (1990, 1993), which were used during the framework analysis. The definitions will later be discussed in light of the analysis and some adaptations in the wording are made to target the definitions directly at nonadherence. Changes in labelling of the constructs will be needed if the constructs are to be used in adherence research. Currently the constructs of errors, violations and mistakes are highly value-laden and may therefore not be appropriate when discussing patient nonadherence (Barber, 2002).

In order to code according to Reasons framework the 'end goal' and the 'correct process' to reach the end goal also have to be defined, in particular to be able to differentiate between mistakes and violations. There are some difficulties with defining the end goal and correct process due to the dual perspectives of the patient and the health care providers (HCPs), which will be discussed in section 3.5.1.2 on page 214. For the purpose of the analysis, however, the end goal was defined as 'achieving optimal treatment outcome' and the process of getting there was defined as 'adhering to the treatment as prescribed'.

TABLE 6 DEFINITIONS OF CONSTRUCTS OF THE ACCIDENT CAUSATION FRAMEWORK THAT WERE USED IN THE ANALYSIS

Structure from Reason's Framework	**Definition**
Latent Conditions – *Level of the Organisation*	Underlying conditions within organisational structure that encourage nonadherence, e.g. management decisions, poor communication, poor monitoring, deficient training.
Nonadherence producing conditions – *Level of the Task / Environment*	Direct reasons and causes of nonadherence, including misperception of risk, poor feedback, poor human system interface.
Violations – *Level of the Individual*	Deliberate acts violating the correct process towards reaching the end goal.

	• Routine violations: cutting corners wherever opportunity arises. • Optimising violations: actions taken to further personal rather than task oriented goal or optimise some goal other than safety. • Exceptional violations, also called necessary or situational violations (Reason 2001): actions that seem to offer the only path available to getting the job done, and where rules and procedures are seen to be inappropriate for the present situation. • Sabotage: violations where adverse consequences were intended.
Knowledge based mistakes – *Level of the Individual*	Actions may go to plan but the plan is inadequate to reach desired outcome. Knowledge based mistakes arise when encountering a novel problem where no pre-existing solution exists and the patient (needing to use on-line reasoning) use an incomplete or incorrect mental model of problem.
Rule based mistakes – *Level of the Individual*	Actions may go to plan but the plan is inadequate to reach desired outcome. Rule based mistakes arise when encountering a familiar problem, but using the wrong solution; including misuse of good rule or use of bad rule.
Slips, lapses & fumbles – *Level of the Individual*	Plan might be adequate, but was not executed as it was intended. Slips & lapses are failures related to attention and memory, e.g. forgetting & strong habit intrusion (the more automatic the behaviour becomes, the more likely are slips and lapses). Fumbles was also mentioned in Reason 2001 paper as an execution failures, but was not directly discussed or defined.
Defences	Defences are measures designed to protect against hazards (and to mitigate the consequences if an accident has occurred). • Protection: to provide a barrier between hazards and potential victim under normal operating conditions. • Detection: to detect and identify the presence of abnormal conditions or

	presence of hazards. • Warning: to signal the presence and the nature of the hazards to all those likely to be exposed to danger. • Recovery: to restore the system to a safe state as quickly as possible. • Containment: to restrict the spread of the hazard after an event has occurred. • Escape: to ensure the safe evacuation of potential victims.

3.3.3 DATA PREPARATION AND ANALYSIS

The interviews were tape-recorded and transcribed verbatim. The transcripts were analysed using a framework approach; a qualitative method of analysis developed specifically for applied and policy relevant research that is driven by theory (Ritchie and Spencer, 1994, Ritchie et al., 2003). The framework approach was thus chosen because the aim of this piece of work was to test the applicability of an existing framework to explain nonadherent behaviour.

Framework analysis has previously been used in health care research, in particular when the focus of the research is driven by policy related issues that are explored from a system wide perspective. For example, Griffiths et al (Griffiths et al., 2001) explored reasons for increased risk of hospital admissions of people with asthma, which included a wide focus of patient's internal reasons as well as factors within the health care system. The study found that the reasons included personal factors such as adherence to treatment recommendation and poor self-management, as well as system factors such as access to care and the patients' confidence in HCPs (Griffiths et al., 2001). Other examples of research that have used the framework approach include analysing barriers to accessing care for Asian women experiencing mental distress, self-harm and suicide (Chew-Graham et al., 2002), views of stakeholders on genetic testing for complex diseases risk (Carter et al., 2006) and barriers to accessing cardiac rehabilitation services (Tod et al., 2002).

Framework analysis is a process in five stages:

1. Familiarisation – data transcription and further familiarisation by reading transcripts and notes in order to list new ideas and themes
2. Identifying a thematic framework – identifying of key issues, themes and concepts to code the data. The goal is to produce a detailed index of the data, which can be used to divide data into manageable chunks that can subsequently be retrieved and explored
3. Indexing – applying the thematic framework to the transcripts systematically and coding all data
4. Charting – rearranging the data according to the framework in charts, which should contain distilled summaries of views and experiences
5. Mapping and interpretation – the charts are used to define concepts, map out nature and range of the phenomena and find associations between concepts that might explain the findings.

Steps 1 and 2 of the framework analysis are very similar to the initial coding stages that were performed for the general constant comparison approach used in the analysis of the interview data in chapter 2, with the exception that *a priori* questions and issues would have been allowed to influence the coding. It was therefore assumed that performing these two steps again would result in largely the same sub-themes identified in the analysis of chapter 2, in particular since the researcher would inevitably be influenced by the '*a priori knowledge*' from having worked for several months analysing the same data according to this coding system. Consequently it was decided that the sub-themes that had already been identified in the interview data would be the basis of this framework analysis (Table 7, pp. 181).

However, in order to be able to chart the sub-themes according to the ACF additional information was retrieved directly from the original transcripts in regards to the patients' reasons for forgetting doses. In addition, detailed descriptions were retrieved in regards to patients' strategies for taking imatinib by using routines and prompts. Extracting this additional information from the interview transcripts was done because the current analysis of charting the sub-themes according to the ACF requires this degree of detail.

In step 3 the ACF was applied to indexing this data. This indexing step tests the usefulness of the ACF to explain the themes and sub-themes related to CML patients' adherence behaviours.

In step 4 the sub-themes and related patient quotes were charted in an excel spreadsheet with each rows representing a participant and each concept from the ACF represented by a column. Each cell included information on the relevant sub-theme/s, a summary of the related quote/s and markers of the interview and line number, which direct the reader to the relevant section in the interview transcript. This step is done to make the data transparent and accessible to all the people in the research team (and anyone else interested in accessing the data) and to facilitate interpretation.

Finally, in step 5, the analysis was interpreted and the usefulness of the ACF to explain nonadherence was evaluated.

All analysis was performed by the chief investigator (LE). Reliability of the analysis and coding framework used in step 1 and 2 was discussed in chapter 2, section 2.3.5 (pp. 100). To ensure reliability step 3 of the framework analysis was separately conducted by a second researcher (NB). The indexed data was compared and thoroughly discussed between LE and NB, any discrepancies were resolved by discussion. Subsequent step 4 and 5 was carried out by the chief investigator, but a meeting was held by the research group (LE, SC and NB) to discuss the findings.

3.4 RESULTS

3.4.1 META CATEGORIES, THEMES AND SUB-THEMES OF ADHERENCE RELATED BEHAVIOURS

The meta-categories, themes and sub-themes from the analysis are presented in Table 7 below.

TABLE 7 RESULTS FROM CONSTANT COMPARISION ANALYSIS (CHAPTER 3): META CATEGORIES, THEMES AND SUB-THEMES USED FOR POST-HOC ANALYSIS

Meta categories	Themes	Sub-themes
1 Nonadherence	1.1 Unintentional nonadherence	Apparent reason: Forgetting because of tiredness
		Apparent reason: Forgetting because failed to plan forward (to bring meds)
		Apparent reason: Forgetting because of distraction / CHANGE of routine
		Apparent reason: Forgetting because IT IS routine / automatic
		Apparent reason: Forgetting GENERAL
		Apparent reason: Accidentally taking too much
		Apparent reason: Hard to swallow tablets
		Apparent reason: Vomiting tablets back up
		Apparent reason: Prescribing error
		Apparent reason: No imatinib available at pharmacy
		Changed dose: Lost/dropped tablet
		Frequency of unintentional nonadherence
		Hard to remember if taken or forgotten
	1.2 Intentional nonadherence	Apparent reason: Because of side effects
		Apparent reason: Because of socialising/dining out/drinking alcohol
		Apparent reason: Because of travelling

	Apparent reason: Because of diversion from planned activities
	Apparent reason: Because of temporary illness (flu/bug/cold)
	Apparent reason: Because of risk of pregnancy
	Apparent reason: Because of negative emotions and feelings
	Apparent reason: Because of "no real reason/lack of discipline"
	Apparent reason: Because of bad taste
	Changed dose
	Frequency intentional
	Contemplating future nonadherence
1.3 Overlapping Intentional & Unintentional nonadherence	Apparent reason: Bad taste
	Apparent reason: Tiredness
	Apparent reason: Forgot then could not be bothered
1.4 Consequences of nonadherence	Perceived consequences
	Conflicting information re consequences
	"Getting away with it"
	Reliance on monitoring and HCPs to detect and relay changes in clinical parameters
	Don't think missing the odd dose make a difference
1.5 Action taken by patients in response to nonadherence	Compensating for missed doses
	Do not compensate for missed doses
	Changing routine to avoid nonadherence
1.6 Positive reinforcement	
1.7 Influence of trial procedures on	

	nonadherence	
2 Adherence	2.1 Reasons for being adherent	Because the Dr say so/conformist
		Patient's responsibility to adhere as prescribed
		Imatinib keeps me alive
		Want treatment to work on reduced dose
		'Reformed nonadherer'
		Do not experience side effects
		Faith in HCPs / imatinib
		'All or nothing person'
		Understanding of how illness and treatment works
	2.2 Awareness of HCPs desire for adherence	
	2.3 Never nonadherent	
	2.4 Do not forget	
	2.5 Have not changed dose	Tempted to change dose
3 Medication management	3.1 Change over time	Becoming relaxed with taking imatinib as responding well
	3.2 No change over time	
	3.3 Late doses	
	3.4 Strategies for taking imatinib	Routine: Meds taken with food
		Routine: Obsessive re taking meds
		Routine: Split dose
		Routine: Crush and dissolve in water
		Routine: Counting tablets
		Routine: Chew tablets
		Routine: Do not mix with alcohol
		Routine: Habits (automatic behaviour / habit to put it off)

Routine: Wanting to take the full dose in one go

Routine: Meds taken in the morning

Routine: Meds taken in the evening

Routine: Planning forward (take meds with if going out/take meds early if going out/for holiday)

Prompts: Dosette box

Prompts: Keep supply in many different places

Prompts: TV program

Prompts: Keep meds in kitchen (visual prompt)

Prompts: Keep meds in bathroom (visual prompt)

Prompts: Meds left visual (visual prompt)

Prompts: Alarm (mobile/watch)

Prompts: Morning reminds

Prompts: Family – nagging reminding

Prompts: Meal reminder – meds paired with meal

Meds kept in meds cabinet

No strategy

3.4.2 EXPLAINING NONADHERENCE USING THE ACCIDENT CAUSATION FRAMEWORK

Table 8, summarises the results from the framework analysis by showing the subthemes indexed according to the constructs of the Accident Causation Framework. Note that for prompts and routines the individual sub-themes have not been listed due to space restrictions in the summary table. The data show clearly that slips and lapses, and violations, were the most common forms of nonadherence in this patient group. The analysis also revealed a range of reasons, or 'nonadherent producing conditions', that the patients expressed as causing their nonadherence, including tiredness, distractions, side effects and the belief that missing a few doses would not impact on clinical outcome. Latent conditions were only inferred from the data, but it was apparent that models of communication between HCPs and patients, patient education and certain organisational failures had made nonadherence more likely to occur. The patients also mentioned a range of defences they had used to support their adherence, including the use of prompts and routines for taking the imatinib as prescribed. Finally, two categories could not be explained by the ACF and were categorised separately. These exceptions will be addressed in the discussion section.

TABLE 8 INTERVIEW SUB-THEMES CHARTED ACCORDING TO THE ACF

Slips / Lapses / Fumbles	Violations - informed decision, understanding what is the right thing but choose not to	Knowledge based mistakes/decision (Key is "Novel - has not encountered the problem before")	Rule based mistakes/decision (key is "has encountered the problem before & has set rule")	Nonadherence producing conditions	Latent conditions	Defences	Do not fit
				INFERRED			
Apparent reason: Forgetting because of tiredness	Apparent reason: Side effects = Optimising violation	Reason: Because of temporary illness (flu/bug/cold)	Reason: Because of travelling	Tiredness, change of routine, distraction, habit intrusion, poor forward planning		Protection: Meds management: Strategies for taking meds - Routine	Unintentional reason: Hard to swallow tablets
Apparent reason: Forgetting because of distraction / CHANGE of routine	Apparent reason: Travelling = Optimising violation	Reason: Because of risk of pregnancy		Unintentional reason: Prescribing error	Organisational failure	Protection: Meds management: Strategies for taking meds - Prompts	Unintentional reason: vomiting tablets back up
Apparent reason: Forgetting because failed to plan forward (to bring meds)	Apparent reason: Socialising/dining out/drinking alcohol = Optimising violation	Changed doses		Unintentional reason: No imatinib available at pharmacy	Organisational failure	Recovery: Compensate for missed doses	
Apparent reason: Forgetting GENERAL	Apparent reason: Diversion from planned activities = Exceptional violation			Side effects	Inherent product characteristics	Recovery: change of routine	
Apparent reason: Forgetting because IT IS routine/automatic = Habit intrusion	Apparent reason: Negative emotions and feelings = Optimising violation			Perceived consequences	Models of communication HCP - patient; Patient education	Adherence reasons for being adherent	
Apparent reason: Accidentally taking too much	Apparent reason: Bad taste = Optimising violation			Conflicting information re consequences	Models of communication HCP - patient	Detection: Perceived consequences	
Hard to remember if taken or forgotten	Apparent reason: Travelling = Optimising violation			Reliance on monitoring and HCPs to detect and relay changes in clinical parameters	Models of communication HCP - patient; Patient education		
Apparent reason: changed dose due to lost/dropped tablet				Don't think missing the odd dose make a difference	Communication HCP - patient; Patient education		
				Positive reinforcement	Models of communication HCP - patient; Patient education		
				Becoming relaxed with taking imatinib as responding well	Models of communication HCP - patient; Patient education		
				Influence of trial procedures on nonadherence	Organisational failure		

3.4.2.1 UNINTENTIONAL NONADHERENCE: SLIPS AND LAPSES

Eleven patients referred to events that were classified as slips and lapses. Most commonly patients described events that caused them to forget to take their imatinib. There were different reasons for forgetting. The following passages present examples of slips and lapses due to a range of different causes.

Tiredness is a common side effect of imatinib that patients have stated as a reason for intentional nonadherence. However, tiredness also seems to indirectly cause unintentional nonadherence as patients commonly attributed their slips and lapses to tiredness. This suggests a causative link between specific side effects, in this case tiredness, and nonadherence. This causative link is possibly mediated by the influence of tiredness on memory and attention processes, as well as motivation.

> ...I am tired and just go to bed, and you know, sometimes I would be lying in bed, awake, just before I go to sleep, and think – oh actually I haven't taken my pills. So I go Yeah got to take them. But obviously, so maybe if I fall asleep I could easily forget... [Patient 11: line 60]

Other patients experienced slips and lapses due to attention failures caused by changes in the routine and 'habit intrusion'. The intention to take the imatinib was interrupted and the patient continued to perform other habitual behaviours, thus forgetting to take the medication.

> ...Usually your mind is on something else and you are just kind of running about doing something and then all of a sudden dinner is ready and you are thinking about something else. It's usually a complete forgotten thing... [Patient 7: line 133]

Another example of nonadherence caused by attention failures were when the behaviour of taking the imatinib had become habitual and was thus carried out on "autopilot", which meant patients found it hard to remember if they had taken the medication or not.

> ...Earlier it was easier, but later on it does get difficult to remember [to take the imatinib because] It's just routine. You are just on autopilot, you're not thinking that you are doing it... [Patient 10: lines 70-74]

Forgetting whether a dose had been taken or not could lead to missing doses, as well as leading to over dose with imatinib:

> ...I took them, and then half an hour later I took them again. I had a mental block for some reason... [Patient 19: line 62]

The patient above had completely forgotten and simply repeated the act of taking the medication, and not until after this was done did the patient realise an extra dose had been taken. The patient immediately called the hospital and was told there was no immediate danger of having taken this double dose.

However, in situations where the patient became aware of the inability to remember whether a dose had been taken or not they seemed more reluctant to take an extra dose than to miss a dose.

> ...Well, if I think I've missed it I will definitely wait until the next day. I might well have taken it, but if I think I've missed it, rather than overdose... [Patient 15: line 115]

This appears to be because the patients perceive the risks of over dosing to be more dangerous than missing doses. This suggests the patients are aware of the narrow therapeutic index of imatinib (and thus high toxicity), which may have been influenced both by acquired knowledge, as well as having experienced, or observed other patients', side effects. Patients who had not experienced severe side effects often expressed their 'luck' for tolerating imatinib well in the interviews.

Patients also mentioned that at times the slip or lapse was caused by a failure in planning forward, for example the patient forgot to take the imatinib with them when going out or when staying overnight away from home.

> ...Yes, there have been times when we've gone to relatives houses and decided to stay there, last minute, and I haven't had any on me ...//... I used to leave a couple at other people's houses, in case, but I don't really do that much anymore... [Patient 21: line 215]

What is particularly interesting with the quote above is that the patient used to have a method to manage this cause of unintentional nonadherence. However, since then the patient has abandoned this method as a consequence of communication with health care providers downplaying the impact of missing doses.

Finally, a patient referred to missing doses as an accident, consistent with the argument of using the ACF to explain patients' reasons for missing doses of imatinib.

> ... I'm sure there's times when it was an accident where it just gets to, you know, just forget... [Patient 11: line 49]

3.4.2.2 UNINTENTIONAL NONADHERENCE: FUMBLES

A category that has not got much attention by Reason in developing the ACF is 'fumbles'. This category was briefly mentioned in Reason's 2001 paper, but not defined or explored to the same extent as the rest of the framework. This may be because fumbles are less related to psychological processes than slips and lapses, or maybe because fumbles are generally less common in areas where the ACF has been implemented. Nevertheless, one patient referred to having to take a reduced dose because he had lost the tablets when having been out, and this incident seems to be best described as a fumble.

> ...I think I did once, when instead of the five I took four. Mainly because I was away and I'd lost one of the tablets. So that's the only reason why I would not take the five that I usually take... [Patient 19: line 74]

3.4.2.3 UNINTENTIONAL NONADHERENCE: PRESCRIBING ERROR AND ACCESS TO IMATINIB

There were two examples of unintentional nonadherence that cannot readily be categorised according to the accident causation model's taxonomy of nonadherence, namely nonadherence due to prescribing error and nonadherence due to restricted access to imatinib. These two examples were in the analysis charted as 'nonadherence producing conditions', discussed in section 3.4.2.8.

> ...There was an error in the prescribing, from the point of view of three months, or two months, as it was then versus the appropriate number of days ...//... so I was one pill short... [Patient 1: lines 67-71]

> ...There was a spell when [the pharmacy] had no medication for me, so I went for nearly a week with no medication... [Patient 18: line 41]

However, the reason these two examples does not fit the error/nonadherence taxonomy is that they would be classified as errors directly if these were discovered within a general error analysis of a health care system (and we had not defined the error as equal to nonadherence). This issue will be discussed further in section 3.5.1.3 (pp. 216).

3.4.2.4 UNINTENTIONAL NONADHERENCE: PROBLEMS WITH SWALLOWING OR TREATMENT INDUCED VOMITING

Two patients gave specific examples of problems with swallowing tablets. Even though this might initially have led to unintentional nonadherence, the patients had found strategies to deal with this problem. One patient chewed the tablets, the other patient did currently experience less problems as the imatinib tablets he is prescribed are now smaller. Previously, the patient used to crush the imatinib, mix it with water and drink it. The imatinib tablets are film coated, which is supposed to protect the tongue from unpleasant taste. The film is quickly broken down when in contact with liquid (such as saliva or liquids in the stomach) and there is no known effect on bioavailability or absorption to crush or chew the tablets on ingestion. However, the taste of imatinib is reported to be disgusting; hence the

same underlying condition that initially led to unintentional nonadherence instead caused the patients to choose to not take their imatinib due to the bad taste.

Furthermore, several patients referred to nausea, which most often led to intentional nonadherence. However, at times the patients would take the imatinib and quickly become ill and vomit the tablets back up, this would be classified as unintentional nonadherence. Depending how long it takes between ingestion and vomiting different amounts of the imatinib is going to have been absorbed. However, it can be assumed that a large part of the dose would not have been absorbed. As in the example above, it is likely that in the beginning of treatment this more often led to unintentional nonadherence due to an inability to keep the tablets down. However, over time the patient developed "a feeling" for when they would be sick and in these circumstances would rather miss the dose.

> ... I know when I feel ill, if I am going to take the imatinib and I know there's a 90 percent chance that I'm going to be sick, and out will come the iron, and all the other good stuff that I have taken. Then it's sensible, I think, not to take it... [Patient 04: lines 725-727]

The intentional nonadherence due to bad taste or nausea can be explained using the ACF as a violation. However, unintentional nonadherence caused by a physical problem (inability to swallow tablets or induced vomiting) cannot be explained using the ACF. In discussion section 3.5.1.3 I will suggest how the framework could be adapted to also account for physiological factors which hinders adherence and an argument for why this is an appropriate modification will be presented.

3.4.2.5 INTENTIONAL NONADHERENCE: KNOWLEDGE BASED MISTAKES

Knowledge based mistakes were apparently infrequent amongst the patients in this sample, with only 4 examples from 3 different patients brought up during the interviews. Knowledge based mistakes are arising when dealing with an entirely novel situation and the action taken leads to interruption in the process towards achieving the end goal, in this case the decision to not take the imatinib as prescribed. The lack of these types of mistakes amongst these patients might therefore be due to the fact that all the patients had been taking imatinib for at

least 2 years and have thus previously encountered most situations in which they may decide to not take their imatinib as prescribed.

It is also possible that the fact that the patients who were interviewed were all treated at a specialist teaching hospital, that is a 'centre of excellence' for the treatment of CML, meant they received a lot of support and clarity regarding the 'right' way to take the imatinib and what to do in different circumstances. The two scenarios that were classified as knowledge based mistakes were nonadherence due to temporary illness, such as the flu or a cold, and nonadherence due to the possibility of being pregnant.

> ...I had a sort of fluey, buggy, thing, for a while and I tried taking 400 [this patient was at the time prescribed 600mg od], but it didn't make any difference. So I did stop taking it for a week... [Patient 17: line 71]

> ...I just thought, weighing it up, I am better off not taking Gleevec in case I am pregnant, for two weeks, because it won't make that much difference, than risking being pregnant and maybe having a miscarriage again, because I've taken Gleevec ...//... I didn't tell [my doctor] and I didn't tell anyone really. I just did it... [Patient 13: lines 90-93]

A few weeks later when she was sure she was not pregnant she continued the imatinib treatment, and never informed her clinician of the treatment interruption. The reason this example was classified as nonadherence is that the patient never sought advice from her clinician during this period, which would have been the correct process in this situation. However, her nonadherence was the correct response as women currently are not recommended to take imatinib during pregnancy as there is an increased risk of birth defects (Pye et al., 2008). It could therefore be argued her nonadherence should instead have been classified as an exceptional violation.

3.4.2.6 INTENTIONAL NONADHERENCE: RULE BASED MISTAKES

Rule based mistakes were also rare in this group of patients. Rule based mistakes arise in situations that are similar to previously encountered situations and a rule

has been formed of how to deal with that type of situation. However, the rule that the patient has developed is considered inappropriate as it leads to interruption of the treatment regime. The reason that rule based mistakes were so rare are most likely due to similar reasons as mentioned in the previous section such as receiving treatment at a 'centre of excellence' may mean that rules of how to deal with different circumstances relating to adhering to imatinib may be very clearly explained. The only example of a rule based mistake came from a patient who had a rule of not taking the imatinib when travelling across time zones.

> ...My job occasionally makes me travel to the west coast of the United States or Europe, and there's the time zone thing, and you just think you don't want to take it when you are travelling ...//... It just seems to be more of a logical thing not to... [Patient 07: lines 113-119]

3.4.2.7 INTENTIONAL NONADHERENCE: VIOLATIONS

In contrast to knowledge and rule based mistakes, violations were very common amongst the patients that were interviewed. Violations are deliberate actions that interrupt or alter the process towards achieving the end goal, even though the correct process is known. The following section will explore the range of different situations that led the patients to choose to alter or discontinue their imatinib treatment.

3.4.2.7.1 ROUTINE VIOLATIONS

Routine violations of cutting corners wherever opportunity arises were not directly represented in the sample. You could argue that patients who regularly missed doses because they did not think it would matter if they missed "the odd dose" were cutting corners because they perceive there is an opportunity to do so. However, the specific examples given by patients regarding their reasons for nonadherence were better explained by optimising and situational violations.

3.4.2.7.2 OPTIMISING VIOLATIONS

Optimising violations were the most common violations represented in this sample. The definition of optimising violations is to further personal goals rather

than safety. In regards to adherence this translates to the patients 'violating' the prescribed treatment by missing doses to further personal goals of improving quality of life and to reduce side effects, whilst the possible safety issues in regards to reducing clinical benefit are overlooked.

Dealing with side effects was indeed the most common reason for the patients to "optimise" the treatment regimen from a quality of life perspective (which is very different from "optimal clinical benefit", which I use throughout the thesis to describe the best possible treatment outcome). The patient below gave an example of how expectations based in previous experiences of the drug effects can lead to a violation.

> ...After all these years your body tells you if you take imatinib now, you're going to be sick, no matter what happens you're gonna be sick, and so when I feel like that I leave it out and I take it the next day... [Patient 4: lines 189-193]

Many patients tended to "optimise" their treatment regime when they were socialising with friends, in particular if drinking alcohol; either to cope with side effects or out of convenience.

> ...If I wanted to socialise and have a few alcoholic drinks then I wouldn't take it then, as well, because they made me feel worse by doing that... [Patient 11: line 57]

The quote below is from a patient who sometimes did not take the imatinib when having been out with friends out of convenience, but the underlying reason was that the patient had to eat to reduce nausea side-effects of taking the imatinib. It was thus preparing the food that was the primary inconvenience and not the act of taking the imatinib.

> ...If we've been out and we've come back later than expected, say eleven o'clock at night, I am not about to go and have a couple of rounds of sandwiches just to take the tablets... [Patient 20: line 64]

Another patient would not take the imatinib the day after he has been drinking alcohol because when he 'feels bad in the morning' does not like to take it.

> ...If I've had a beer the night before, I won't take it. Sometimes I take it later in the day. But we met some people on Saturday night we hadn't seen for a long time, and I had a couple of beers, and I just got to [Sunday] lunchtime and thought – oh I'll leave it now... [Patient 17: lines 62-64]

This patient only experienced nausea after taking imatinib very rarely and is not able to link the nausea with any particular circumstances, saying that it might only be when he has "picked up a bug or something" [Patient 17: line 40]. One patient "optimised" her treatment regimen to improve quality of life when she experienced negative emotions and feelings.

> ...I don't feel right that night for a particular reason, I won't take it because I know it'll aggravate how I'm feeling... [Patient 2: lines 618-620]

The quote below represents a patient who chewed the imatinib because of trouble swallowing whole tablets and he therefore "optimises" his treatment regime by missing doses when he does not feel like having the bad taste of chewing the tablets in his mouth.

> ...[I do not take my imatinib if] I've eaten something too recently and I just don't really want to have that taste in my mouth that evening. But it's very rare that I do that. Most evenings I just take it. I would say no more than three times, four times a month max... [Patient 12: line 27]

Similar to rule based mistakes, a patient gave an example of an optimising violation that was due to travelling; in this case the patient was going on holiday. The difference between the travelling example that was classified as rule based mistake, and the example given below, is that the rule based nonadherence of patient 07 was due to regular travelling with work and as a rule the patient would not take the imatinib when travelling across time zones 'because it was a logical

thing to do'; whereas Patient 17 felt the need to go on holiday without having to deal with side effect.

> ...I went [for a holiday] last year, and I did actually stop taking the tablets for the week before I went, because of the tiredness. 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, so you are talking about ten days... [Patient 17: line 113]

3.4.2.7.3 EXCEPTIONAL VIOLATIONS

Exceptional violations, also called situational or necessary violations, are actions that seem to offer the only path available and other rules and procedures are seen as inappropriate for the present situation. This was represented in the interviews by nonadherence caused by a diversion from already planned activity.

> ...We originally planned to go for a meal afterwards but we never went for the meal, so rather than take it without a meal I decided not to take it... [Patient 07: line 103]

3.4.2.7.4 SABOTAGE

Sabotage is a group of violations where the adverse consequences were intended. There were no examples of direct sabotage of the imatinib treatment regimen. However, one patient told the story of sabotaging the treatment regime that was first prescribed when diagnosed with CML in order to fit the patient profile and get selected for participation in an imatinib trial.

The patient was diagnosed at a time when imatinib was not yet licensed as first line treatment in the UK. The patient had researched to find out the best available treatment as well as where to receive the best health care. Based on this research the patient had identified a highly esteemed Professor who was leading the imatinib trials at the Hammersmith at this point. The patient decided that the only way forward was to see this Professor and to get admitted onto the imatinib trials.

However, it turned out that only those patients with a particular illness response profile were admitted to the trials:

> ...Well, basically they looked for people who had funny levels, up and down, up and down. My levels were not quite like that. So I just didn't take the drugs I was taking at the time correctly. I took a lot one day, none the next day, none for a week, then a few, so I knew my levels were going to be all over the place, because that's the sort of people that were going into the trial, and it worked... [Patient 13: line 133]

The patient thus managed to sabotage the original treatment response to the effect that the illness profile of patients who were still admitted to the trials was achieved. As a consequence the patient was enrolled into the imatinib clinical trial. At the end of the interview the patient described the day the first round of imatinib was dispensed:

> ...I tell you, when I first got it, the first package of Imatinib; I came to London to pick it up, it was like I had a piece of gold in my handbag. If somebody had nicked my handbag that day, they could have had everything, my credit cards, my money, anything, but I would have just asked them to give me the drug. And that's how I feel about it. To me it's very, very special. I have got a very good relationship with Gleevec. It's a good thing in my life, definitely... [Patient 13: line 169]

3.4.2.8 NONADHERENCE PRODUCING CONDITIONS

Nonadherence producing conditions are conditions under which nonadherence becomes more likely, including slips/lapses, mistakes and violations. It is evident that the patients experience a range of different reasons that seem to produce or encourage nonadherence. Table 8, on page 186, displays nonadherence producing conditions that were identified in the interviews.

3.4.2.8.1 UNINTENTIONAL NONADHERENCE

The conditions that underlie slips and lapses are failures that influence memory and attention. As already mentioned, the conditions that encourage the occurrence of slips and lapses include change of routine, tiredness, distraction, habit intrusion and poor forward planning. The example of a fumble, the patient who dropped a tablet, could not be linked to a particular condition that was influencing the patient.

As mentioned above in section 3.4.2.3 prescribing error and failure to supply imatinib could be classified as nonadherence producing conditions. However, the nonadherence resulting cannot be classified according to the current categories of errors/nonadherence (i.e. slips/lapses/fumbles, mistakes and violations) because the abovementioned conditions directly caused nonadherence independent of the patients' behaviour. The ACF could be adapted to account for this type of cause of nonadherence and will be discussed further in section 3.5.1.3.

3.4.2.8.2 INTENTIONAL NONADHERENCE

In this section we will analyse the factors that seemed to encourage mistakes and violations in this patient group, which we class as intentional nonadherence. In relation to errors and accidents it has been argued that mistakes mainly arise from informational problems such as incomplete knowledge; whilst violations are generally associated with motivational problems and perceived lack of concern (Reason 2001). Nevertheless, the most important condition underlying intentional nonadherence in this study, including both mistakes and violations, was side effects. Patients have to deal with side effects in everyday life, as well as in a range of specific situations

There were a range of other conditions that seemed to encourage violations that were mostly related to a general lack of understanding of the risks associated with missing doses. For example, many patients said that it does not matter if you miss "the odd dose"; a belief that in many cases seemed to have been reinforced by feedback the patients had been given by their doctor (second quote below).

> ...Well, I think, maybe if you miss one or two every now and again, I don't think it's going to make a big deal, that's why I missed it. Because I felt better in myself. So I thought – well, have a day off and I'll feel better because of it... [Patient 11: line 52]

> ...I'd done this thing a month before [patient had stopped on clinician's advice because of side effects] and knew that if I stopped taking them I was going to feel better. And so that was why I did it ...//... And both sets of specialists have sort of said to me it won't make any odds if you miss a few. And that was the first time I did it, it was last May... [Patient 17: line 208]

One patient who had a MEMS adherence <85% mentioned the information leaflet that comes with the imatinib as the source that made him not worry about missing doses.

> ...I wouldn't have thought it would have had that major impact [to miss doses]. I mean, reading the paperwork you get with the tablets, it says take it as soon as you realise, and just get back into the routine... [Patient 10: line 88]

Some patients started to be nonadherent after they had had a period off imatinib on the advice of a clinician and did not perceive any adverse consequences from this planned treatment interruption.

> ...Well, I stopped taking [imatinib] to conceive and then I was off it for like seven months ...//... So I thought – blimey, I'm off it all this time, and actually it's not making a lot of difference. And all of a sudden after nine or ten months it started to shoot up, my blood count, it was coming back and so I had to go back on [imatinib]. But then when I restarted it I thought: well, maybe I can be a bit more blasé about taking them almost. I don't need to be so rigorous, because I came off it ...//... and it didn't seem to make much of a difference for the first seven months anyway. So part of me probably thought that actually if I miss a few it's not going to be a major deal... [Patient 11: lines 144-146]

A similar incident would be if the patient experimented with missing doses without informing their clinician and did not perceive an impact on clinical response. This may be due to the clinicians tending to focus on positive feedback. However, it can also be that patients receive different levels of feedback depending on how detailed they like their feedback to be. Some patients have note books were they note all their blood counts and PCR results, and follow closely their clinical response. Whereas other patients do not want this level of detail, but prefer that the clinicians simply tell them whether they are doing well or not. It is possible the patients who are more interested in receiving detailed clinical feedback are also more likely to be adherent with a good response. This would mean that the patients who could be considered most in need of receiving feedback because their clinical response is not as good as it 'should be', are less likely to receive this feedback.

Nonetheless, patients also expressed a reliance on clinical parameters to detect adverse consequences of their nonadherence, and were confident their clinician would relay such consequences if detected.

> ...Obviously the PCR test would pick it up pretty quickly if it was started to move in an adverse direction... [Patient 1: line169]

> ...I suppose if they noticed that there was something wrong then they would say, you know, make sure you take the full dose... [Patient 9: line 56]

Patients may also receive conflicting information from different HCPs regarding the potential consequences of missing doses.

> ...Well, I've had two conflicting comments about that. One is - look, it doesn't matter too much if you miss the odd one dose, and that is what I have generally been told. I think generally, if I was to miss a day, I don't think it would be the end of the world ...//... [On the other hand the] professor said that the issue with missing it on a day ...//... is that you do have that twenty four hour window when there is a chance for the cancer to spread a little bit ...//... [However,] I have on a number of

occasions been told that it doesn't matter, if I was to forget any drugs. Once ...//... I needed to get hold of [imatinib] so I got in touch with [the local hospital], to see if I could come in and get some, and they said: Look, we just had a chat with the doctors and they've said it doesn't matter if you missed a weekend, it's absolutely fine ...//... I know that's not the only example, but it's the only one that I can actually give a vivid example of right now... [Patient 14: lines 88-94]

3.4.2.9 LATENT CONDITIONS

Latent conditions are failures at the level of the organisation and constitute the underlying organisational processes that create an environment where errors or nonadherence are more likely to occur. These processes include management decisions, poor communication, poor monitoring and deficient training. Latent conditions can only be inferred from this data and the results were displayed in Table 8 on page 186.

There are five areas of latent conditions that seem to have encouraged the occurrence of nonadherence in this patient group:

1. Inherent product characteristics causing side effects
2. Models of patient-health care provider communication and feedback of clinical data
3. Patient education
4. Organisational failures related to prescribing and access to imatinib
5. Product development

The latent conditions give some guidance of where to focus future interventions for imatinib; in particular targeting intentional nonadherence. Certain latent conditions may be difficult to change, such as the product characteristics that cause side effects. However, it may be possible to provide support for patients to cope better with side effects, such as co-therapy that can be given to reduce side effects or other types of support.

As discussed in the introduction chapter communication is thought to be one of the most important factors related to the HCPs that may influence patients' adherence to treatment (Alexander et al., 2006, Osterberg and Blaschke, 2005). Communication, in particular feedback on clinical response and information about risks of missing doses, also seemed to have reinforced nonadherent behaviours in several of the patients who were interviewed. There were examples of patients' preconceived ideas about what roles the patient and the health care provider play in the treatment system, as if there are implicit contracts of what responsibility the patients should take to adhere to their treatment.

> ...And [whether I take my imatinib or not] is not something I've been specifically asked either. I think the assumption is this is your medicine, you have been prescribed to take at this rate per day, you know, it's up to the patient to take responsibility for that. And maybe if you really weren't responding at all they might ask more searching questions into why that might be the case... [Patient 20: lines 89-90]

The quote also suggests that there is little communication between the patients and the HCPs in regards to whether the treatment is followed or not. Nonetheless, changing the model of communication between HCPs and patients, including clinical feedback and information, may have a positive effect on reducing intentional nonadherence and may be an area where improvements are achievable.

In some cases it is possible that if patients knew the impact that a few missed doses, such as 3/month, can have on their clinical response they may be motivated to improve their adherence.

> ...If I thought there was going to be any effect on it then I guess that would make a big difference ...//... if I miss the odd one, once a month or twice a month or whatever it works out, it doesn't seem to affect my overall counts or anything like that... [Patient 19: lines 91-92]

This suggests that patient education, and possibly also making the clinicians more aware of the potential consequences of relatively few missed doses, may reduce

nonadherence. As discussed in the introductory chapter of this thesis, however, it should be noted that it was first in 2009 that a study on adherence to imatinib that showed an association between nonadherence and reduced clinical response (Noens et al., 2009). In turn, our study that was published in early 2010 was the first study to demonstrate that the cut-off point in adherence below which it is likely to have a significant impact on clinical response was 90% (Marin et al., 2010). Therefore, it is possible that the problem of nonadherence to imatinib, and the clinical implications this can have, are becoming more common knowledge. This may already have instigated some change in how nonadherence issues are approached in clinical practice, at least in some hospital settings.

Organisational failures leading to lack of imatinib in stock at the pharmacy is an area where improvements seem to be achievable. Another incident which was inferred to stem from a latent organisational failure was the example of a prescribing error:

> ...[I missed taking my imatinib] because there was an error in the prescribing, from the point of view of three months, or two months, as it was then versus the appropriate number of days... [Patient 1: line 67-69]

However, when rethinking the incident at the point of interpretation it was realised that maybe the incident was not directly caused by a 'prescribing error', but it might have been another organisational failure that caused this incident of unintentional nonadherence, namely a failure of communication. When attending the clinic the patient would normally be given the prescription in the consultation and is then told by the clinician to go and book their next appointment at the reception desk, often with the instruction of booking an appointment when available "in 2 months" or "in 3 months", thus it is very easy an appointment is booked so that the patient is a few days short of imatinib. However, we do not know how common these kinds of failures are and how much they affect adherence to imatinib.

Product development is another area that is more difficult to intervene in to make changes after the finished product has already been marketed. However, some

changes in the formulation of the imatinib have been made during the 10 years it has been available. For some patients the availability of smaller tablets has aided their adherence to the imatinib treatment.

> ...[Imatinib] used to come in really big tablets, and I couldn't swallow them, so I used to have to smash them up and pour them in water, which was really bad cause it burnt. But now they are in smaller tablets, so it's a lot easier ...//... they manufactured, instead of 800 it was two fours. So I could swallow them. It was fine. So that solved that problem... [Patient 21: lines 65-69]

3.4.2.10 DEFENCES

Defences are measures designed to protect against hazards; in the case of nonadherence these would correspond to measures that can minimise the risk of nonadherence. The defences that will be discussed in this section are protection, detection, warning, recovery, containment and escape. Please refer to Table 6, page 176, for definitions.

3.4.2.10.1 PROTECTION

In relation to nonadherence, protection could be defined as measures that minimise nonadherence and promote adherence. It seems that protection in general would primarily be suited to reduce unintentional nonadherence.

In relation to the patients who were interviewed, protections included direct prompts such as dosing boxes (e.g. Dosette box) and alarms that helped the patients remembering to take the imatinib. Protections also consisted of more indirect prompts, for example through pairing the act of taking the imatinib with another daily act, such as a regular meal or a daily TV program.

> ...I have a little box [to help me remembering to take the imatinib] and you have Monday, Tuesday, Wednesday, Thursday ...//... I've had this one for years ...//... and I fill them up once a week... [Patient 5: lines 417-429]

...I have a system where I have a watch that has an alarm and when the alarm goes off I take my pill, basically... [Patient 14: lines 68-71]

...I just take it after my dinner. I eat a meal every evening, so therefore I just don't forget... [Patient 16: line 62]

Protection also included forming routines and habits that made it easier to remember to take the imatinib.

...After being on [imatinib] two years it's like routine now, you know. If I am going out at night I take my tablet before, if I am staying at mum and dad's it comes in toiletry bags... [Patient 18: line 120]

3.4.2.10.2 DETECTION

Detection of nonadherence is essential in order to be able to address the problem. In general, detection is only possible after the nonadherence has occurred, either by monitoring nonadherence directly or by monitoring clinical parameters that are known to be affected by nonadherence. Detection systems should then ideally feedback to the clinical team, the organisation and the patient, so that any causes can be addressed and hopefully nonadherence can be reduced.

The quote below is an example specifically related to imatinib of a nonadherent patient who was told about his MEMS results from the trial during his clinical appointment. Because of this the patient got the opportunity to discuss the underlying issues for his nonadherence (difficulty dealing with side effects of a 600mg dose). As a result the clinician decided to reduce the dose to 400mg and the patient thus reported less side effects and an increase in self reported adherence during the interview.

...they gave me a pot of drugs to monitor how many I was taking, and when I brought it back, actually, I had been missing quite a lot of days. Like, I knew I was missing days, but I didn't quite realise how many I was missing. So it worked out that maybe I'd missed twenty percent of the doses over a three month period. So it wasn't working quite as well as it could do, so they said – we'll bring your dose down instead, to

400mg, make sure you take it every day. And the side effects haven't been quite so bad. So it's more manageable to do that... [Patient 11: lines 34-35]

3.4.2.10.3 WARNING

In relation to nonadherence there can be two specific warning systems, one is to predict which patients are likely to be nonadherent and the other is to detect patients who are already nonadherent. In both cases the system would identify patients who may need support to adhere better to their treatments.

In CML patients, nonadherence has a negative effect on their clinical response indicated by the PCR increasing (Marin et al., 2010). However, it is likely to take several months before an increase in PCR results are large enough to signal a warning of a patient's nonadherence. Below is a story of how one patient was apparently nonadherent for 2 months before her PCR results signalled a warning to several different HCPs at two different hospitals that she was not adhering to her imatinib.

...when I stopped taking it, it was after I had been to [the local hospital] and then they left me 6 weeks ...//... Afterwards I had to go to [the specialist hospital] and that was when I got a phone call, saying 'oh your PCR has gone up', because it was totally nil, she said 'have you stopped taking the drug?' ...//... Funny enough I'd gone to [the local hospital] that day and the phone rang and it was [the doctor] from [the specialist hospital] who was able to speak to the doctor [at my local hospital] telling him that my PCR had gone up, and they spoke on the phone and spoke to me and said, 'excuse me are you taking [the imatinib]' and I said 'well, I am now'.

LE: So you didn't consult anyone before you did it?

P: No

LE: Was it not until they started notice that something was going on?

P: Yeah, and also in a way I was a bit, I thought, not that I wanted to see how long it would going up, but it was interesting to find out within two months it started going up... [Patient 2: lines 254-274]

3.4.2.10.4 RECOVERY

Recovery is about restoring the system to safe levels as quickly as possible and could, in relation to nonadherence, include instances where the patient compensates for missed doses upon realising doses have been missed. Only two patients mentioned that they tended to compensate for missed doses, whereas nine patients said they would not compensate for doses missed. The patient who is quoted below normally takes the imatinib in the evening.

...Yeah, if I've missed it I always take it first thing in the morning. I don't know if you are meant to, but I just kind of think, well, rather than miss the whole day, first thing in the morning, and then sort of, I take it a bit later that night. If I have got up and taken it at eight o'clock in the morning then I take it nine, ten o'clock at night... [Patient 18: line 110]

3.4.2.10.5 CONTAINMENT

Containment does not seem to be useful when analysing nonadherence to imatinib in CML patients. Nonadherence cannot directly spread between one nonadherent CML patient to another; in particular not unintentional nonadherence. Intentional nonadherence, on the other hand, which is influenced by patients' beliefs and motivations, may be influenced through potential informal discussions and advice between patients (as well as patient support groups, online forums and websites).

However, patients have the right to discuss their illness and treatment with whoever they wish to talk to and it would not be right to restrict this potential communication; even though at times patients may have a different view of taking or not taking their treatment as prescribed compared to HCPs. Similarly, adverse consequences from nonadherence (i.e. reduced clinical benefit) cannot spread between patients in the case of CML.

However, these concerns may be viewed differently if using the ACF to analyse nonadherence to treatment of infectious diseases such as HIV or tuberculosis where consequences of nonadherence can affect the population at large.

3.4.2.10.6 ESCAPE

Escape and safe evacuation of potential victims is a type of defence that does not seem applicable when analysing nonadherence to imatinib in CML patients. It is also unclear whether this particular defence mechanism would be applicable when analysing nonadherent behaviours in other illness groups.

It can be noted that protection, detection and warning are all in line with the original pictorial models of the ACF where defences are situated between the error and the accident (Figure 21, pp. 170). However, recovery, containment and escape are per definition only possible after the accident has occurred; this is in contrast to the pictorial frameworks presented by Reason (1990; 2001). This will be discussed further in the section on adaptations 3.5.1.3 (pp. 216), where adaptations of the ACF will be suggested.

3.5 DISCUSSION

The ACF (Reason 1990) appears to adequately explain patients' reasons for intentional and unintentional nonadherence. The results of this analysis show that virtually all reasons described by CML patients for not taking their imatinib as prescribed can be explained by the ACF's constructs. Slips and lapses explained unintentional nonadherence where the patient intended to take their imatinib as prescribed but was hindered to do so, most commonly due to forgetfulness for different reasons. Intentional nonadherence was in this study mainly due to violations and the most frequent reason for patients to violate their prescribed treatment regimen was to deal with side effects.

There were in this group of patients very few examples of unintentional fumbles, as well as intentional rule and knowledge based mistakes. Fumbles were mentioned in Reason's paper from 2001, but is generally lost amongst other constructs, rarely defined other than being 'an execution failure' and often not

mentioned at all. In the current analysis the single example of a fumble was a patient who dropped one of the tablets and therefore had to take a reduced dose on that occasion.

It is understandable that there were few examples of knowledge based mistakes in this sample because all the patients had been on imatinib for at least 2 years. Knowledge based mistakes arise in response to novel situations where no previous knowledge or rules of how to deal with the situation exist and the patient has to rely on online reasoning, which for some reason leads to a mistaken response (nonadherence). Since these patients would have encountered and dealt with most situations before participating in the study, it is not a surprise that knowledge based mistakes were rare. Following the same reasoning it would be likely that knowledge based mistakes would be more common in newly diagnosed patients first prescribed imatinib; a hypothesis worth exploring to advance the use of the ACF to explain nonadherence in other patient groups. Finally, the hospital where these patients were treated is a 'centre of excellence' for treating CML in the UK. It is therefore possible that these patients receive more thorough care and support, and that rules for the imatinib regimen is more clearly described, compared to other hospitals in the UK; thus patients may be better informed than patients receiving care from other hospitals. Hence, knowledge based mistakes may be more common in other hospital settings.

There was only one example of a rule based mistake in this patient group; a patient who did not take imatinib as prescribed when travelling across time zones. Rule based mistakes occur when dealing with previously encountered situations where a rule of how to deal with these situations have been formed based on incomplete or mistaken knowledge. The lack of rule based mistakes is likely to be because patients tend to know two important rules. First, the correct process of taking their imatinib (e.g. 400ml once daily, 600mg twice daily); most patients appear to understand that this process does not change across different situations. Second, most patients understand that they are likely to die if they discontinue their imatinib therapy without being prescribed another treatment regime (except missing 'the odd dose'). If a patient knows the correct process but chooses not to follow it the resulting nonadherence would always be classified as a violation

according to the ACF. It seems rule based mistakes are more common amongst elderly patients prescribed chronic medication in primary care (Barber et al., 2005), which could be because these patients have less knowledge about their specific illnesses and related treatments and often prescribed multiple medications. Furthermore, the consequences of not taking these medications may not be immediately life threatening.

Analysing nonadherence according to the ACF revealed a range of nonadherence producing conditions that seemed to encourage the occurrence of nonadherent behaviours, such as the frequent side effects of imatinib and a general tendency amongst patients to underestimate the potential adverse consequences of nonadherence. The data also allowed for the inference of underlying latent conditions that provide an environment where nonadherence is more likely to occur, including failures in communication between health care provider and patients and patient education.

Vincent (Vincent, 1998) have applied the ACF to health care and have suggested merging the 'latent factors' and 'error producing conditions' into seven main factors when analysing clinical incidents (Table 9). However, the pictorial taxonomy is identical to Reason (1990) with higher level 'latent conditions' including institutional, organisational and management factors, and the rest of the factors being grouped under 'error producing conditions' one level down (followed by errors and violations, defences and accident). These seven main factors may be useful to consider when furthering research using the ACF to understand causes of nonadherence. In particular as it suggests where other factors that we know affect nonadherence, such as cognitions and beliefs, may fit into the ACF. Evidently, in terms of nonadherence, the patient would be both 'the patient' and 'the individual', so these two factors would merge.

TABLE 9 THE ACF'S CONCEPTS OF ERROR PRODUCING CONDITIONS AND LATENT CONDITIONS MERGED INTO SINGLE FRAMEWORK WITH 7 MAIN FACTORS TO EXPLAIN CLINICAL INCIDENTS (ADAPTED FROM VINCENT, 1998), AND HOW THIS MAY CORRESPOND TO THE FACTORS EXPLAINING NONADHERENCE

Main factor	Applied to clinical incident	Applied to adherence
Patient factors	Medical condition, language, personality	Medical condition, cognitions & beliefs physical abilities, knowledge, skills
Task factors	Task design, decision-making aids, availability & use of protocols	Treatment characteristics
Individual (staff) factors	Knowledge, skills, health	
Team factors	Communication, supervision, leadership	Communication between HCP & patient, clinical feedback, monitoring
Environment	Workload, skill mix, equipment	Patient's environment & daily life, social support etc
Organisational and management	Financial resources,& management, policy, standards, safety culture	Financial resources & management, policy, standards, safety culture
Institutional context	NHS executive, regulatory context	NHS executive, regulatory context

The interviews also included a range of examples of defences taken by patients to promote adherence, in particular protective measures of using prompts and forming routines to facilitate the use of imatinib. Understanding how latent conditions and nonadherence producing conditions promote nonadherence give some clues as to where we should focus interventions, in particular to address intentional nonadherence. Whereas a better understanding of defences and may be more directly linked to address unintentional nonadherence.

3.5.1 APPROPRIATENESS OF APPLYING THE ACCIDENT CAUSATION FRAMEWORK TO EXPLAIN NONADHERENCE

The Accident Causation Framework has proven useful in explaining nonadherence. In addition, by taking the system perspective of addressing the issues of nonadherence we are moving away from holding the patent solely responsible for nonadherence and are reducing the blame directed towards nonadherent patients. Instead research is focused on understanding the factors within the system that

affect nonadherence and on working towards solutions to address these factors. This blame free approach signifies one of the advantages with using the ACF and is meant to encourage people in general as seeing nonadherence as a normative behaviour and therefore report on instances of nonadherence openly.

However there are a number of issues that need to be addressed in order for the ACF to be appropriate in analysing nonadherent behaviours, which will be addressed in this section:

1. Terminology needs to be adjusted to be less value laden. As has been pointed out previously, it is not appropriate to refer to patient behaviours as errors, mistakes and violations (Barber, 2002, Barber et al., 2005).
2. There might be some divergence between what HCPs and patients consider the 'correct process' and the 'end goal' of the prescribed treatment.
3. There were some examples of reasons for nonadherence from the interviews that could not be explained according to the ACF. However, the argument will be put forward for two adaptations that will allow the framework to explain all examples of nonadherence from the interviews.

This section will conclude by presenting a novel adaptation of the ACF that may be better suited to explain nonadherence.

3.5.1.1 TERMINOLOGY

The terminology used in the field of medical errors is derived from studies of manufacturing and industrial process, where right and wrong processes are clearly defined. Therefore, the language is highly value laden and refers to 'failed' actions as errors, mistakes and violations.

The reference to error was already dropped when conducting the analysis for this chapter and was replaced by 'nonadherence'. In this way 'error producing conditions' were referred to as 'nonadherence producing conditions'. Mistakes can also straightforwardly be replaced by 'nonadherence' without influencing the definitions (Table 6, pp. 176); thus 'rule based mistakes' and 'knowledge based mistakes' can instead be referred to as 'rule based nonadherence' and 'knowledge

based nonadherence'. It is more difficult to find an appropriate label for 'violations'. Violations are deliberate deviations from the correct process although the correct process is known, and include routine violations, optimising violations, exceptional violations and sabotage (Table 6).

It can be argued that these four types of violations would have had to be preceded by some conscious reasoning or deliberation by the patient before taking the decision to not follow the treatment regime correctly. This could suggest replacement labels such as 'reasoned' nonadherence, 'deliberate' nonadherence or 'rationalised' nonadherence. Nevertheless, to avoid semantic confusion of the definition of the acts which are currently referred to as 'violations' the definitions of these three words were obtained and carefully considered before deciding (Table 10). Of the three suggested words 'rationalise' seemed the more appropriate to explain the act of violating a prescribed treatment regimen considering the type of nonadherent behaviours that the construct is meant to explain, such as exceptional acts of nonadherence justified by a specific situation or acts to optimising (reorganise) the process of taking imatinib. Therefore, violation will instead be referred to as rationalised nonadherence. The perspective of the rational is that of the patient.

TABLE 10 SUGGESTED WORDS AND DEFINITIONS TO REPLACE THE LABEL OF 'VIOLATIONS'

Word	Definition*
Reason	Think, understand, form judgement logically
Deliberate	Engage in long and careful consideration
Rationalise	Attempt to justify (an action or attitude) with logical reasoning; reorganise (a process or system) to make it more logical and consistent; make (a company or industry) more efficient by dispensing with superfluous personnel or equipment.

*Definitions obtained from the Compact Oxford English Dictionary online (Oxford, 2010)

3.5.1.2 DEFINING THE CORRECT PROCESS AND THE END GOAL

There may be some divergence between what HCPs and patients would see as the end goal of treatment and what the correct process to achieve the end goal would be. In industrial settings the end goal is usually clearly defined and the process of achieving the end goal is often strictly controlled; thus right and wrong actions can be determined.

In relation to a health care treatment regimen the process and end goal are more difficult to define and may be different depending on whose perspective is considered: the patient's or the health care provider's. In essence both parties could be assumed to strive towards achieving as good treatment outcome as possible. From the HCPs' point of view, often encapsulated as the 'biomedical world view', the process of achieving this is simply for the patient to adhere to the treatment regimen as prescribed; assuming the correct diagnosis has been made and that the prescribed treatment is appropriate. To some extent the patients' view is similar, in particular as the patients I interviewed had already consented to be included in a trial that investigated adherence, side effects and clinical response. However, from the patients' point of view there may be other factors that complicate the process of achieving a 'good' treatment outcome, such as day to day quality of life.

The tendency for people to prefer immediate, but 'discounted' benefits instead of future increased benefits (e.g. prefer immediate quality of life on the cost of future clinical benefit, although quality of life then may in the future be worse) has attracted researchers trying to predict health behaviours on basis of peoples' time preferences; the extent to which people discount future benefits for immediate benefits (Chapman, 2005). However, even though time preferences has been shown to predict general health behaviours, e.g. students use of alcohol and cigarettes (Daugherty and Brase, 2010), as well as preventive health behaviours such as attending genetic testing for the risk of breast cancer (Gurmankin Levy et al., 2006); there is little evidence that time preference is associated with adherence to chronic medication (Chapman et al., 2001, Elliott et al., 2008).

Nonetheless, it was clear from the interviews that many patients skipped imatinib doses when the need to alleviate side effects and improve quality of life took priority over adherence to therapy. In some cases the patient did understand that the nonadherence could have a negative effect on their response, but still chose to not take the imatinib. However, it was also evident that many patients did not appreciate the potential adverse consequences of their nonadherence. Indeed some patients said that they would not skip doses if they thought it would affect their response negatively. It can thus be assumed that most patients would define their end goal as achieving as good a clinical response as possible. Nonetheless, for patients who experience side effects the process of reaching this goal includes occasional nonadherence when necessary to improve quality of life.

Recent research has shown that an adherence rate of at least 90% is essential to reach the, according to HCPs, ultimate end goal of imatinib therapy: the complete molecular response (CMR) where no further leukaemic cells can be detected in the body (Marin et al., 2010). Furthermore, as already mentioned in chapter 1, reaching and maintaining CMR over a period of time may constitute a cure for some patients (Rousselot et al., 2007, Mahon et al., 2002). It is possible that if patients know there is a chance of a cure by achieving CMR they would also consider CMR as the ultimate end goal of treatment. These two pieces of evidence thus allow for better definitions of the treatment process and the end goal of treatment that patients and HCPs may agree over. This knowledge may not affect adherence rates per se; patients would still have to deal with the same issues. However, it could inform psychological interventions primarily aimed at helping patients to cope with side effects and coping may be more achievable if the patient has a potential 'end date' where further treatment (and the related side effects) is no longer needed.

In addition, it has allowed us to better define the correct process and end goal of treatment for future research of adherence to imatinib using the ACF. Consequently, the end goal of imatinib treatment is defined as achieving CMR and the correct process to reach this end goal is defined as adhering to imatinib at a rate of 90% or above. The task for future research would be to develop interventions to support patients through the process of adhering to therapy.

3.5.1.3 ADAPTATIONS

The current Accident Causation Framework as adapted to nonadherence (Figure 23, pp. 174) could not account for CML patients' reasons for unintentional nonadherence to imatinib caused by prescribing error, access to medication or problems with swallowing tablets. These types of reasons for unintentional nonadherence are likely to also be experienced by patients on medications for other chronic illnesses. This suggests that there are some updates needed before the ACF can adequately explain all reasons for nonadherence, both in the specific case of imatinib and in chronic medications in general. The suggested adaptations will be discussed in the following sections and concluded by presenting a new ACF adapted to nonadherence.

3.5.1.3.1 SYSTEM FAILURES

The Accident Causation Framework cannot account for prescribing error and access to imatinib as reasons for nonadherence, which are factors that are likely to generally apply in terms of adherence to other treatments as well. This is because the framework originates from industrial setting where these two examples would have been explained as errors in themselves, i.e. the prescribing error would be analysed in terms of the acts of the prescriber and the system influencing this act and the restricted access to imatinib would have been seen as a supply failure. Therefore these errors would have been seen as 'someone else's error', which would never have to be explained in the context of patients' cognitions and actions.

The ACF therefore needs to be adapted to be able to account for these factors, such as prescribing error and access to treatment, that are in effect causes of nonadherence that are not medicated by patients' cognitions and actions. Figure 24 (pp. 221) shows the updated framework. It can be seen that two boxes 'intended action' and 'unintended action' have been added, these two boxes direct all causes of nonadherence that in the end have been mediated by patients' cognitions and actions. In addition there is one arrow that shows the direct influence of 'nonadherence producing conditions' on unintentional nonadherence, which will be classified in the nonadherence taxonomy as 'system failures'. These

system failures are thus shown to not be mediated by patient cognitions and actions.

3.5.1.3.2 CONSTRAINTS

Problems with swallowing tablets can currently not be explained by the ACF. There is simply no construct to account for physiological barriers of performing an act. The reason for this is probably because a person who physically cannot perform a certain action would within an industrial or organisational setting never be hired to perform such an action in the first place. For example, a person missing both arms would not be hired to pull a lever.

In contrast, patients who have been prescribed a certain treatment may physically not be able to take their medication; swallowing tablets is only one example as research has shown a range of other physiological barriers in other illness groups related to dexterity such as problems opening a pill bottle or using a medication device (Horne et al., 2005). We have thus shown the need for a construct to account for unintentional physiological causes of nonadherence within the ACF, if the framework is going to funny explain nonadherence. In addition, a possible explanation for why this construct was never included in the original framework has been put forward. Figure 24 (pp. 221) display a proposed adapted ACF that can explain nonadherence, which can explain nonadherence to imatinib and is likely to be appropriate to explain nonadherence to other medications in other illness groups.

3.5.1.3.3 DEFENCES

In Reason's original Accident Causation Framework (Figure 21, pp. 170) defences are defined as measures designed to protect against hazards and to mitigate the consequences if an accident has occurred (it is noteworthy, however, that the second part of the definition that defences can be 'to mitigate the consequences if an accident has occurred' are never represented in the pictorial models of the framework). Figure 23 (pp. 174) proposed how the framework was adapted to nonadherence to form the theoretical base of the analysis of this study. There it was suggested that, in terms of explaining nonadherence, defences, would be better depicted as a barrier between the nonadherence producing conditions and

the intentional and unintentional nonadherence, imagining that defences would generally be interventions to deal with nonadherence.

Nonetheless, having analysed the data there were several examples of defences and it became apparent that they would be situated in several places throughout the system of the framework. Indeed, there were examples of patients use of certain defences to reduce unintentional nonadherence, such as dosing boxes and alarms, corresponding to 'protection' situated between the nonadherence producing condition and unintentional nonadherence. However, there was also an example given of how the patient's nonadherence had been detected because of the monitoring of adherence rates during the trial, this had warned the clinician what was going on, who in turn had fed back to the patient during a clinical appointment.[1] This had in turn led to causes having been addressed and the patient reported increased adherence. This suggests there is a place for defences, in particular 'detection' and 'warning' as a barrier between 'nonadherence' (both intentional and unintentional) and 'reduced clinical benefit'.

The interview data revealed one more example of 'detection' and 'warning', however, and that was a patient who had stopped for several months without telling anyone. The patient had been repeatedly asked by different HCPs whether the treatment was taken as prescribed or not, but not until the clinical response took a significant adverse turn (indicated by an increase in the clinical parameter 'PCR', which measures residual leukaemia in the body) did the patient finally tell the HCPs about the missed doses and started taking the imatinib tablets again. This suggests that there should be a third level of defences situated after 'reduced clinical benefit' has occurred; again this level seems to mainly correspond to 'detection' and 'warning'.

In both the examples of the patient whose nonadherence was detected and addressed and of the patient whose reduced clinical benefit was detected and addressed, the result was to try and restore adherence to imatinib. This can be

[1] I do not know how or why this happened, but I assume it was because the patient asked about his trial results. As far as I know no other nonadherent patients from the trial have been told of their trial adherence rates.

seen as the defence mechanism of 'recovery'. Therefore, recovery would mainly be situated in the level of defences that are between nonadherence producing conditions and intentional and unintentional nonadherence. In all the above mentioned cases there seems to have been a feedback loop informing both HCPs and patients of the occurrence of nonadherence and clinical consequences.

3.5.1.3.4 FEEDBACK LOOP

As discussed in the previous section, there are two defences concepts of detection and warning. These defences seem to have acted as a feedback loop that passed on information about the occurrence of nonadherence and impact on clinical benefit to higher levels of the system (e.g. health care providers) and it is suggested that this feedback loop should be clearly represented within the pictorial representation of the Accident Causation Framework (ACF). This feedback loop would be dependent on accurate monitoring of outcome variables, such as adherence rates and clinical outcomes, which can be fed back to higher levels of the health care organisation. In addition, detection and warning of adverse effects may also influence the patients' behaviour through self-appraisal, as proposed by Leventhal (1992). In these examples, the feedback loop seems to have had a positive effect on the patients' adherence rates, which suggests the benefit of continuously monitoring adherence rates as part of clinical practice.

3.5.1.3.5 NONADHERENCE PRODUCING CONDITIONS

Nonadherence producing conditions (or "error producing conditions") is an integral part of the original ACF (Reason 1990). As has been discussed previously, in relation to nonadherence this level of the framework (Figure 24, pp. 221) explains the causes of intentional and unintentional nonadherence. The examples included in Figure 24 are environmental factors (e.g. access to medicines), psychological factors (e.g. beliefs about illness and treatment, and depression) and physiological factors (e.g. problems with swallowing), as well as illness and regimen specific factors (e.g. side-effects). Therefore, the level of nonadherence producing conditions allows us to integrate other explanatory factors that have been related to nonadherence. This is very useful as areas such as beliefs about medicines have been found to be associated with and predictive of adherent

behaviours in many illness groups (Horne et al., Clifford et al.), and should therefore be accounted for by future explanatory models of nonadherence.

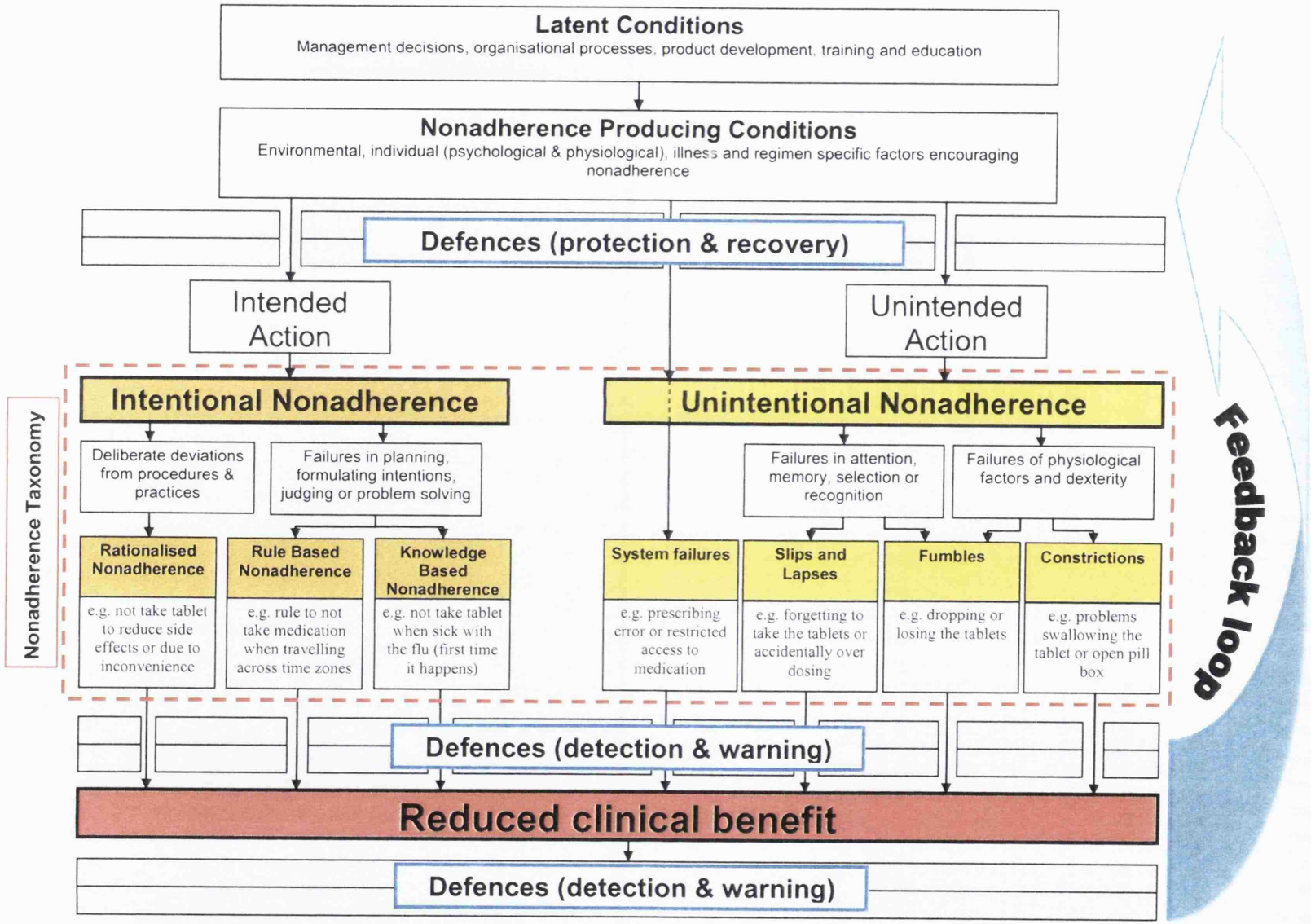

FIGURE 24 THE ACCIDENT CAUSATION FRAMEWORK WITH CONSTRUCTS AND TERMINOLOGY ADAPTED TO NONADHERENCE

3.5.2 LIMITATIONS

This was a qualitative study of a small sample of CML patients prescribed imatinib who were treated at a 'centre of excellence' in the UK, thus the findings are therefore not generalisable to other illness and treatment populations.

The data that was analysed in this chapter were derived by semi-structured in-depth interviews. Had the interviews instead been theory driven it might have been possible to derive more specific details useful for the classification of the data according to the ACF. For example, even though the researcher went back to the original transcript to derive additional details for this post-hoc analysis, several quotes regarding forgetting are grouped under a 'general forgetting' code. Further probing during the interviews into the specific situations surrounding these slips and lapses may have benefited the analysis. Theory driven interviews could also have probed for further information regarding latent conditions that the patients may have experienced.

Although the adapted ACF appears to adequately explain nonadherence to imatinib therapy, further quantitative research is needed to test the framework components association with nonadherence. In addition, even though the framework appears to explain factors associated with nonadherence in general, this study cannot directly be used to support the use of the ACF to explain nonadherence to other treatment and illness groups without further research.

A final limitation is related to the use the framework to further explore nonadherence. That is there are currently no existing instruments, such as questionnaires or measurements that operationalise the concepts from this framework in relation to adherence. Such instruments would need to be developed to further research in this field.

3.5.3 FUTURE RESEARCH

To further inform the theoretical development of the framework it would be advisable to map out the whole system influencing nonadherence to medication. For example, by interviewing different stakeholders within the system, such as

pharmacists, clinicians, reception staff that book appointments, managers and policy developers, a clearer picture of the complete system is likely to emerge.

Similarly, if the framework is to be applied in a new illness or treatment groups it is always advisable to initiate the research by a thorough qualitative exploration of the factors that may influence adherence in this specific group to see whether the ACF seems to be a useful explanatory theory.

Furthermore, in order to test the ACF's ability to explain and predict nonadherence, future research should include developing questionnaires that operationalise the different concepts of the ACF. In addition, ideally measurements of adherence rates should be developed in line with the ACF, to support further adherence research using this framework.

Finally, if the ACF seems the appropriate explanatory theory for nonadherence in a particular group it can be used to develop adherence enhancing interventions. The ACF has the potential of being superior to other theories in designing adherence enhancing interventions as it allows for both intentional and unintentional causes to be addressed, as well as addressing wider system factors that are beyond the patients' immediate control.

3.5.4 CONCLUSIONS

The Accident Causation Framework has been shown to be useful in explaining nonadherence to imatinib therapy and has potential to be useful in explaining nonadherence in general. The advantage of defining nonadherence as a medical error explained by the ACF is the possibility of analysing the whole system when working towards solutions; to explain both intentional and unintentional reasons for nonadherence; to avert blame and responsibility from the individual patients; and to promote openness in reporting instances of nonadherence. The analysis revealed that in some instances there has evolved a feedback loop within the system that seemed to have influenced adherence rates. To further support this type of monitoring, feedback and improvement, chapter 4 of this thesis will present the development and piloting phases of a new adherence scale that is specifically suited for continuous monitoring of adherence rates over time.

Chapter 4: The Diagnostic Adherence Scale

BACKGROUND

For the work reported in this chapter, Sara Garfield and Lina Eliasson have had equal involvement in designing, piloting and revising the diagnostic adherence scales (DAS-specific and DAD-multi). All data was cleaned and analysed by Lina Eliasson. Sara Garfield is a senior research fellow at the School of Pharmacy, University of London.

4.1 INTRODUCTION

An important aspect of taking a system approach to understand the causes of patients' nonadherence, as discussed in chapter 3, is to address solutions from a system wide perspective. As discussed in the introduction, current policy drivers have identified finding solutions to reduce treatment nonadherence as a priority for the NHS in the UK (Nunes et al., 2009). However, finding solutions to reduce the incident of nonadherence require both appropriate theory and measurements to drive the development of behavioural change interventions (Campbell et al., 2000, Craig et al., 2008) and to support implementation of evidence based practice recommendations (Michie et al., 2005). This chapter focuses on appropriate measurements and presents the development and piloting of two versions of a new adherence measurement scale that have been developed in accordance with the Accident Causation Framework (ACF; Reason 1990).

Chapter 3 concluded that the ACF, the theory most frequently used to explain medication errors, allows us to understand patients' reasons for nonadherence from a system perspective. Taking a system perspective to understand nonadherence has the advantage of widening the focus from solely patient related factors that explain nonadherence to the impact that system factors such as organisation, staff education and product development also can have on individual patients' ability to adhere to treatment. The ACF has the additional advantage,

compared to other theories used to explain nonadherence, as it explains both intentional and unintentional reasons for nonadherence.

Nonetheless, operationalising the ACF in future adherence research and intervention development first calls for the development of appropriate adherence measurements. The introduction chapter section 1.8 gave an overview of the pros and cons of the most commonly used adherence measurements. It was explained that a measure should ideally be continuous, as this can be used to measure incremental changes in adherence rate as well as to dichotomise adherent or nonadherent patients according to a predefined cut-off point. In addition, it was argued that a measure should be able to dichotomise both intentional and unintentional nonadherence as these two types of nonadherence have different causes and therefore require different solutions.

Most adherence measurements, including pill counts, medical records, MEMS and measures of drug or drug metabolites are giving continuous output data, which is suitable to measure change in adherence rates. Of these measures MEMS is often considered to be the 'gold standard' in terms of measuring adherence rates in patients (Arnsten et al., 2001, Osterberg and Blaschke, 2005, Partridge et al., 2002). However, neither MEMS nor any of the other abovementioned measures captures information regarding the patients' reasons for missing doses. Consequently, none of these measures can be used to dichotomise intentional and unintentional nonadherence. Self-report, on the other hand, can capture the patients' reasons for missing doses and are therefore the only measure that can dichotomise intentional and unintentional nonadherence.

Furthermore, self-report is the only measure that is considered an available method for assessing adherence in a clinical context and was the only assessment method to be reviewed and recommended in the recently published NICE guidelines on adherence (Nunes et al., 2009). Therefore, it was decided to investigate suitable self-report measures to be used to measure adherence rates in the context of the ACF. This chapter will thus first discuss the different methods for validating self-report questionnaires, then consider the advantages and limitations

of existing self-report measures and finally present the development and piloting of the two versions of the diagnostic adherence scale.

4.1.1 ASSESSING ADHERENCE MEASUREMENTS

Nonadherence is a construct which is used to refer to a range of different behaviours all related to not following health care recommendations as prescribed. A measurement of nonadherence is therefore not a direct measure of nonadherence, but is only recording (pro- or retrospectively) the occurrence of certain behaviours, which is assumed to represent true nonadherence. Therefore, prior to use, a measurement of nonadherence has to be assessed for ease of use, reliability, validity and diagnostic ability. The following section will explore these concepts and describe the methods used to assess reliability and validity of adherence measurements.

4.1.1.1 EASE OF USE AND ACCEPTABILITY

Ease of use and acceptability is the evaluation of whether the measure is straightforward to understand and whether responders/assessors can easily answer the questions. In addition, acceptability includes assessment of how appropriate they find the questions. Questions need to be worded so that participants do not find them intrusive, annoying or judgemental, and questions that are too upsetting should maybe not be included. It is important to always make it clear that participants are welcome to not answer any questions they do not want to answer. Time is also important so to increase the ease of use and acceptability of a questionnaire it is advisable to keep the completion time to a minimum (Bowling, 2001).

4.1.1.2 RELIABILITY

Reliability is the consistency of the measurement score over time or across persons being tested. There are different types of reliability, which are of variable relevance depending on the properties of the measurement.

Test-retest reliability is relevant for all adherence measurements and it refers to the consistency of the test results when the same person is tested on different occasions, i.e. a person who scores as nonadherent on one occasion also scores nonadherent on another occasion. Evidently test-retest reliability has to be established when stabile adherence rates can be assumed as a difference between test occasions could be due to an actual variance in adherence rate.

Inter-rater reliability refers to the consistency of the test results when different raters are using the measurement to score the same participants' adherence rate. This test needs to be done with very short intervals so that any discrepancies in adherence rate recorded would be due to measurement error and not due to true changes in adherence rates.

Internal reliability, also called internal consistency, is relevant to self-report measurements that consist of a number of items assumed to measure the same construct; for example if there are 3 questions using different wording but that are all supposed to measure the same cause of intentional nonadherence.

In addition to being reliable a measurement has to be valid and the following section will discuss ways to assess validity of a measure.

4.1.1.3 VALIDITY

Measurement validity is closely linked to definitions and is referring to whether a measurement is measuring what it is supposed to measure, as well as whether the measurement can be used to make accurate decisions (Murphy and Davidshofer, 2005). As mentioned previously a measure can be reliable, i.e. giving an identical output time and again, but not be valid because it is not measuring what was intended. A commonly used example is to test intelligence by measuring the circumference of the skull; using the same tape measure the measurement would be identical each time, thus the measure is reliable. However, the circumference of the skull has nothing to do with intelligence; thus the measure is not valid.

Having a sound theoretical base is essential in order to develop a valid measure. Theory is what defines which aspects of behaviour should be measured and what

constructs (or questions) should be used to capture this behaviour. Theory is thus connected to the most basic strategies of establishing validity of a measurement, which is done by examining the measurement content, namely face, content and construct validity (Murphy and Davidshofer, 2005). Face validity is the extent to which a measurement appears to be a reasonable measure by people using the measure (Murphy and Davidshofer, 2005) and is therefore established through peoples' feedback of their experience with using the measurement. Content validity is established through systematic examination of the measurement content by providers within the field, and is particularly relevant when assessing self-report measures.

It is generally recognised that construct validation should be subdivided into convergent and discriminant validation techniques because it is necessary to show both that measures that are theoretically related correlate (convergent) and that measures that are theoretically unrelated do not correlate (discriminant). In relation to an adherence measurement, convergent validity is established by showing that different measures of nonadherence correlate. Discriminant validity is established by showing the lack of correlation between a measure indicating adherence and a measure indicating nonadherence, as well as between intentional and unintentional nonadherence. The establishment of construct validity is essential for all adherence measurements (DiMatteo, 2004b).

Criterion validity refers to the validity of decisions and predictions made based on the results of the measurement (Murphy and Davidshofer, 2005). A criterion is a measure that can be used to determine the accuracy of a decision, which in regards to adherence in its simplest form would be the "true" adherence rate.

There are two main strategies to assess criterion validity, namely predictive strategies and concurrent strategies that both represent ways to correlate the measurement score with the criterion score (Murphy and Davidshofer, 2005). These two techniques are similar, with the main difference that predictive strategies assess the measurement scores at base-line and the criterion score at a later time point and concurrent strategies assess both the measurement and the criterion score at the same time point.

Within adherence research, concurrent validity is arguably the most suitable criterion validity to validate direct adherence measurements, as adherence rates often vary over time and a difference between different measurement occasions may constitute true changes in adherence behaviour. On the other hand, predictive validity can be established through using a consequence of nonadherence as the criterion instead of "true" adherence rate, such as treatment outcome variables. In addition, predictive criterion validity is essential when validating scales designed to predict future nonadherence, such as questionnaires assessing beliefs related to nonadherence e.g. (Horne et al., 1999) and questionnaires assessing barriers to adherence e.g. (Matza et al., 2009).

There are some challenges in assessing criterion validity of adherence measurements. Indeed, it has been argued that concurrent validation of nonadherence measurements is "impossible" (DiMatteo, 2004, pp. 207) because of the lack of a universal "gold standard" adherence measure of "true" adherence rates that other adherence measurements can be calibrated against; in the same way as the criterion validity of a metric weight scale can be established by using a standardised kilo weight. It is true that there are major challenges in establishing criterion validity for adherence measurements, but it should not be deemed impossible. Instead it is necessary to establish suitable criterion measures to validate the new measurement against, including other measures of adherence (e.g. MEMS), illness progression and/or survival rates. In addition, measurements such as pharmacological and biological markers of adherence may also be suitable as criterion measures. Furthermore, triangulation of measures is always useful when establishing validity, which involves using several different measures to validate a new measurement method.

Adherence measures are very often used to classify patients as either adherent or nonadherent and therefore it is important to establish how good a measure is at classifying patients accurately. To assess the diagnostic ability of a test we have to establish the sensitivity and specificity, which will be discussed in the next section.

4.1.1.4 SENSITIVITY AND SPECIFICITY

Adherence measures frequently aim to classify patients into two groups depending on if they are adherent or nonadherent to their prescribed treatments. In the same way as a diagnostic test for some illnesses dichotomises patients into two groups depending on the presence or absence of a symptom or sign, so a diagnostic adherence measure classifies patients according to the presence or absence of signs of nonadherence or according to a pre-defined cut-off point. A method of assessing the performance, or diagnostic ability, of such binary classification tests is to calculate the sensitivity and specificity, which refers to the proportions of adherent and nonadherent patients who are correctly "diagnosed" by the adherence measurement. Using positive and negative to refer to the presence or absence of signs of nonadherence, sensitivity is the proportion of true positives (nonadherent patients) that are correctly identified by the test and specificity is the proportion of true negatives (adherent patients) that are correctly identified by the test (Altman and Bland, 1994a).

For example, of 100 patients say 50 are truly nonadherent and 50 are truly adherent. Using a dichotomising adherence measure we identify 30 of the truly nonadherent patients as nonadherent and 20 as adherent; whilst we identify 45 of the truly adherent patients as adherent and 5 as nonadherent. The sensitivity would thus be calculated as 30/50 = 0.60, and specificity would be calculated as 45/50 = 0.90. Perfect sensitivity and specificity would thus both be 1.

Sensitivity and specificity are closely related to type I and type II errors, as well as positive and negative predictive values, which will be discussed in the next section. Of course the calculations of all the previous mentioned terms rely on the ability to ascertain who is truly adherent and who is truly nonadherent, which is difficult as we have to rely on other imperfect measurements. Some argue that the current gold standard to measure nonadherence is microelectronic measurements/medication event monitoring systems (MEMS), which in that case would be the measure we should use to establish truly adherent and nonadherent patients to assess the performance of other diagnostic adherence measures (e.g. Paterson and Britten, 2005, Arnsten et al., 2001, Osterberg and Blaschke, 2005,

Partridge et al., 2002, Waterhouse et al., 1993, Cramer et al., 1990). However, this is debatable as MEMS can be inaccurate due to patients either removing several tablets at once or opening the MEMS bottle without ingesting tablets. Table 11 illustrates the relation between sensitivity and specificity, type I and II errors and positive and negative predictive values.

TABLE 11 RELATION BETWEEN SENSITIVITY AND SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES, AND TYPE I AND TYPE II ERRORS (PTS=PATIENTS)

		True Outcome (according to "gold standard")		
		Nonadherent	Adherent	
Measured Outcome	Nonadherent	True Positive (TP) = nonadherent pts correctly classified as nonadherent	False Positive(FP) = adherent pts incorrectly classified as nonadherent (Type I error, P-value)	Positive predictive value = TP / (TP + FP) = proportion of nonadherent pts with a positive test result (i.e. scored as nonadherent) who are correctly diagnosed as nonadherent. This measure depends on the prevalence of nonadherence in the specific patient group.
	Adherent	False Negative (FN) = nonadherent pts incorrectly classified as adherent (Type II error)	True Negative (TN) = adherent pts correctly classified as adherent	Negative predictive value = TN / (FN + TN = proportion of patients with negative test result (i.e. scored as adherent) who are correctly diagnosed as adherent. This measure depends on the prevalence of nonadherence in the specific patient group.
		Sensitivity = TP / (TP + FN) = proportion of actual nonadherent pts correctly identified	Specificity = TN / (TN +FP) = proportion of actual adherent pts correctly identified	

Once a measures sensitivity and specificity has been established and we know the proportion of patients being correctly diagnosed as either adherent or nonadherent, we also want to establish the probability a measure is giving the correct diagnosis. To do this we need to establish the positive and negative predictive values of a test, which will be discussed below.

4.1.1.5 POSITIVE AND NEGATIVE PREDICTIVE VALUES

Sensitivity and specificity are measures of the proportions of truly nonadherent and adherent patients who are correctly diagnosed, but it does not give us any information on the probability that a test will give the correct diagnosis. To calculate this probability we need to establish the predictive values of the test. The positive predictive value is the proportion of patients with positive test results

(scored nonadherent) who are correctly diagnosed; and the negative predictive value is the proportion of patients with negative test results (scored adherent) who are correctly diagnosed (Altman and Bland).

If we are using the same example as above, 30 of the 35 patients who scored as nonadherent were correctly diagnosed as nonadherent, giving the proportion of correct diagnoses as 30/35 = 0.86 (positive predictive value). Of the 65 patients who scored as adherent 45 were correctly diagnosed as adherent, giving the proportion of correct diagnoses of adherent patients as 45/65= 0.69 (negative predictive value).

However, in contrast to calculating sensitivity and specificity, the positive and negative predictive values are dependent on the underlying prevalence of nonadherence in the specific patient population where the test is being used. With reduced prevalence of nonadherence in a specific group the positive predictive value decreases, i.e. we can be less sure that a patient who scored as nonadherent is truly nonadherent; and the negative predictive value increases, i.e. we can be more sure that a patient who scored as adherent is truly adherent (Altman and Bland). This dependence of predictive values on the underlying prevalence of nonadherence means that the values may differ between the published studies of the usefulness of a test to where the test is subsequently being used in further research or practice. Positive and negative predictive values for any prevalence can be calculated as displayed in Table 12 (Altman and Bland).

TABLE 12 HOW TO CALCULATE POSITIVE AND NEGATIVE PREDICTIVE VALUES

$$Positive\ Predictive\ Value = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)}$$

$$Negative\ Predictive\ Value = \frac{specificity \times (1 - prevalence)}{(1 - sensitivity) \times prevalence + specificity \times (1 - prevalence)}$$

Self-report measures can be prospective by asking the patient to fill in medication diaries over a period or retrospective by asking the patients to recall and report their adherence rate. Retrospective self-report measures are the most frequently used and least intrusive technique of assessing nonadherence (DiMatteo, 2004b) and are the focus of this chapter. From here on these retrospective self-report measures will be referred to as simply self-report measures.

Self-report is often the preferred method for measuring adherence because it is generally low cost, it is easily administered both in research and clinical practice settings and, if administered correctly, can have high diagnostic sensitivity and specificity (Haynes et al., 2002). In addition, NICE recommended self-report as the only adherence measure that is viable in clinical practice to monitor adherence rates (Nunes et al. 2009).

There are a range of features that an adherence measure should possess to be appropriate for use in research and clinical practice. As previously discussed in-depth, a measure should ideally produce continuous scale data which can measure change in adherence rates over time, as well as being used to dichotomise patients according to whether they are adherent or nonadherent. In contrast, a categorical measure can only be used to dichotomise patients according to whether they are adherent or nonadherent according to a pre-defined cut-off point or according to the presence or absence of a certain behaviour. Consequently, a categorical measure cannot be used to monitor change in adherence rates over time or incremental changes in adherence rates in individual patients. Moreover, as discussed on several occasions in this thesis, a self-report adherence measure should be able to differentiate between intentional and unintentional nonadherence. Finally, a measure to be used in clinical practice should be easily administered, inexpensive and acceptable to patients.

Nonetheless, it is not just missing doses that can have an impact on patients' health, overdosing can also cause adverse consequences, including death; in particular with drugs such as oral anticancer drugs that are highly toxic with narrow therapeutic indexes (NPSA, BOPA). Therefore, being able to measure

nonadherence due to overdosing, as well as missed doses, is an important feature for an adherence measure that may be recommended for wider use in research and clinical practice. Finally, in addition to all the features mentioned above, before a measure can be recommended for wider use it has to be valid and reliable.

Three recent reviews of self-report adherence measurements have been published:

1. A systematic review (MEDLINE, Cinahl and Psychinfo) of studies reporting the development or validation of a generic self-report adherence measure (i.e. not disease specific) published between 1993 and 2009 (Dobbels et al., 2010).
2. A narrative review commissioned by NICE that summarised the evidence regarding pros and cons of self-report adherence measures, which was limited to other literature reviews and systematic reviews (Nunes et al., 2009).
3. A narrative review (Medline, Science and Social Science Citation Index, PsycINFO and Biosis, as well as hand search of a range of published books, journals and "grey" literature; all limited to 1980 or later) of self-report adherence measures suitable to measure change in adherence rate over time (Paterson and Britten, 2005).

Dobbels et al (2010) identified 20 self-report adherence measures. Of these measures 6 included a continuous measure of adherence. However, of these, 4 measures had not reported or had very low reliability and validity. Of the remaining two, one measure was criticised for unclear wording and difficult administration that required training. The remaining measure was a visual analogue scale validated in HIV and lupus patients. Patients were asked to estimate their adherence on a scale of 0% to 100% and were reported to have good reliability and moderate concurrent and predictive validity (Walsh et al., 2002, Koneru et al., 2007). However, neither of the 6 questionnaires could dichotomise intentional and unintentional nonadherence (Dobbels et al., 2010).

The NICE review highlighted the pros and cons of using self-report measures and concluded that self-report is the most suitable measurement method for routine clinical practice, although other adherence measures may be more appropriate in

clinical trials due to the limitations of self-report (Nunes et al., 2009). It was also acknowledged that self-report is the only measure that can capture qualitative information of patients' reasons for missing doses. Inaccuracies in self-report can be caused by recall bias, social desirability and errors in self-observation. In addition, self-report often over-estimates adherence. These biases can be minimised with using specified time frame for recall, wording questions in a non-judgemental fashion and asking about specific behaviours. In addition, patients reporting nonadherence are generally telling the truth (Nunes et al., 2009).

Furthermore, Paterson and Britten (2005) found that there were no questionnaires that were developed specifically to measure change in adherence rates over time, and that many adherence measures included assessments of beliefs and attitudes related to nonadherence that are superfluous for continuous monitoring of adherence rates. It was concluded that there are currently no validated adherence measure that can be recommended for this type of monitoring (Paterson and Britten, 2005).

The reviews presented in this section did not identify any self-report measurements that displayed all the above mentioned criteria of being able to produce both categorical and continuous data, differentiate between intentional and unintentional nonadherence as well as capture patient who have over dosed with the medication. Therefore, it was concluded that there is a need to develop and validate a new adherence measurement that has these properties.

4.1.3 RATIONALE FOR THE CURRENT STUDY

The decision to develop the diagnostic adherence scale (DAS) was made in order to address the limitations of existing measurements, identified in the previous section, in continuously monitoring adherence rates over time. In particular when taking a system improvement approach of supporting adherence enhancing interventions and adherence services within health care systems, such as the different NHS systems in the UK. The following section sets out the aim and objectives of the current study.

4.2 AIMS AND OBJECTIVES

The aim was to develop and pilot a new self-report adherence measurement scale using 7 days recall of medication-taking behaviour, which can be used for either a single medicine or multiple medicines. To reach this aim the following objectives were set up.

1. To develop an adherence scale grounded in theory.
2. To validate whether patients adherence rates for the 7 days preceding clinical appointment are representative for longer term adherence rates.
3. To develop and pilot a diagnostic adherence scale for a single medicine (DAS-specific).
    a. To pilot the assessment of face and construct validity of the DAS-specific.
    b. To assess ease of use and acceptability of the DAS-specific.
    c. To pilot concurrent validity of the DAS-specific against MEMS.
4. To develop a diagnostic adherence scale for multiple medicines (DAS-multi).

4.3 DEVELOPMENT AND PILOTING OF THE DIAGNOSTIC ADHERENCE SCALES

This section will present the development and piloting phases of the two diagnostic adherence scales (DASs). The subsections are ordered according to the natural evolvement of the scales. Accordingly, the section starts with presenting the theoretical basis for the DASs, followed by an explanation of the scales' functionality in calculating adherence rates and dichotomise intentional and unintentional nonadherence. Thereafter the methods and results sections for Pilot A are presented, which validates whether the patients' adherence rate during the 7 days preceding a hospital appointment is representative for longer term adherence rates. After this section the first version of the DAS-specific is introduced. Following on from this are the methods and results sections of Pilot B and Pilot C, which are testing two different versions of the DAS-specific. Finally the DAS-multi is introduced.

4.3.1 THE THEORETICAL BASIS OF THE DAS

The diagnostic adherence scales (DASs) were developed as short self-report questionnaires based on patients' recall of doses missed or extra doses taken during a 7 day period. The measurements have evolved through stages of piloting and revising to two distinct versions; one version measures adherence to a single medication, the DAS-specific; and one version measures adherence to multiple medications, the DAS-multi. This section will describe the theoretical basis of the DASs and the rationale for including the type of outcome data we aimed to capture with the scales.

In line with a system approach to understand nonadherence, the theoretical basis for the DASs is the ACF (Reason, 1990). Previous literature has shown that this framework is useful in understanding nonadherence to treatment (Barber, 2002, Barber et al., 2005). In chapter 3 of this thesis I presented further adaptations to the ACF so that it is better suited to explain nonadherence to medication. Furthermore, the ACF has the advantage, in relation to all other theories used to

explain nonadherence, that it can explain both intentional and unintentional nonadherence.

In addition, taking a system approach to understand the causes of nonadherence is meant to reduce the judgmental inclination of giving the patients the sole responsibility for maintaining their adherence. Instead, the patients are seen as inheritors of a range of both personal and system causes, which trigger nonadherence. The system stance is thus meant to promote openness in reporting any deviations from prescribed treatment, whether it leads to adverse effects on health or not. In this way we aim to better understand how the whole system can be improved (including supporting patients' individual cognitions and physical abilities), which can inform interventions to reduce the causes of nonadherence.

The DASs were developed to support this line of research and is meant to be easily administrable, inexpensive and acceptable to patients. The adherence rate output data is a continuous scale, which means that the scale can be used to measure change in adherence rates over time. Measuring adherence rates is needed to be able to evaluate the effectiveness of adherence services and interventions, as well as monitor patients' adherence rates in clinical practice and medical trials.

In addition, a continuous scale can also be used to dichotomise adherent and nonadherent patients according to predefined cut-off points. This diagnostic feature of the DASs is essential to identify patients in need of adherence support and to make adherence interventions more efficient by targeting interventions towards the patients who need them.

As previously discussed, nonadherence can have both intentional and unintentional causes, and these causes should be addressed by different types of interventions. Therefore, the DASs include items that are meant to dichotomise nonadherent patients according to whether their nonadherence is intentional or unintentional (or both).

The wording of the DASs content is meant to reduce the bias of under reporting nonadherence due to social desirability. The social desirability effect is the tendency for respondents to answer questions in accordance with what is seen as

socially desirable (Murphy, 2005). In terms of adherence, the general perception is that patients should adhere to their treatment and it is perceived as less socially accepted to not adhere. Hence, patients may state that they take their medicines as prescribed, even when they are not doing so. To reduce the social desirability effect, the questions of the DAS are framed in a non-judgemental way to assure the patients that nonadherence is common and most patients miss doses at times. The DASs items therefore use the framing "People often miss taking doses of their medicines, for a whole range of reasons. Thinking of the last 7 days...". This can be compared to the 1986 version of the Morisky adherence scale (which is the most widely used adherence questionnaire) asking "Are you sometimes careless with taking your medicines?" which has a more judgemental tone (Morisky et al., 1986).

Another bias of self-report is recall-bias. The patient may be happy to report nonadherence, but the reporting is inaccurate because of problems remembering the number of doses missed or taken extra correctly. In order to reduce recall bias, the time period the patent has been asked to recall is limited to 7 days. A further argument for using 7 days recall is that asking patients in a non-judgemental way how many doses they have missed in the last 7 days has previously been shown to have good sensitivity and specificity to identify nonadherent patients (Haynes et al., 1980, Haynes et al., 2002). Finally, this method has previously been used in adherence research based in the ACF (Barber et al., 2005, Clifford et al., 2006). Nonetheless, to further validate the use of the 7 days recall period, Pilot A is testing the difference in patients' adherence rates in the 7 days preceding a hospital appointment with overall adherence rates (measured using MEMS).

Table 13 (pp. 241) outlines how to calculate adherence rates and how to dichotomise intentional and unintentional nonadherence using the DASs, as well as providing some explanatory examples. The scales that were used during the pilot studies are displayed later in the text in Figures 28 (pp. 251); 29 (pp. 256) and 30/31 (pp. 265/266). In order to use the DASs to dichotomise adherent and nonadherent patients a pre-set cut-off point would have to be established based on supporting evidence for the minimum adherence rates needed to obtain optimal clinical response to a prescribed treatment.

This section described the theoretical basis for the DASs, which drove the development of the items / questions that were used. In summary, the DASs were developed in accordance with the ACF to support adherence research and practice taking a system approach to find solutions to patients' problems with adherence; in particular to be able to capture changes in adherence rates over time. The DASs items were developed to capture adherence rate on a continuous scale from patients' self-reported 7 days recall of doses missed or taken extra. In addition, specific items were included to capture whether the doses missed or taken extra were done so intentionally or unintentionally. The items were worded to be perceived by patients as non-judgemental and to present nonadherence as a normative behaviour, thus intending to make patients more likely to be comfortable with reporting nonadherence to their treatments. The first version of the DAS can be seen in Figure 27 (pp. 250).

TABLE 13 CALCULATING ADHERENCE RATE AND DICHOTMISE INTENTIONAL AND UNINTENTIONAL NONADHERENCE USING THE DAS

Item taken from DAS-specific used in Pilot B	**Construct/s**	**Example answer**	**Example output**	**Range**
1) What is the prescribed dose of.....?	Prescribed dose	100mg 1/day (1 tablet/ day)		N/A
2) On how many occasions in the last seven days have you missed doses of this medication?	Adherence rate	100mg x 2 (2 tablets)	Tablets taken = 7-2 = 5 Adherence rate = ((5/7)x100)= 71%	Continuous: 0%-100%
3) Below are examples of reasons other people have given for missing doses of their medicines. Thinking of doses of ..... you have missed in the past 7 days, which of the following statements apply to you? I decided it was better not to take it ☐ I forgot to take it ☐ I was unable to take it ☐ Other [Please specify)	Intentional and unintentional nonadherence	P1 ticked 'decided it was better not to take it' P2 ticked 'forgot to take it' P3 ticked 'unable to take it' P4 ticked both 'decided not to take it' and 'forgot to take it'	P1 is classified intentionally nonadherent P2 is classified unintentionally nonadherent Patient 3 is classified unintentionally nonadherent P4 is classified both intentionally & unintentionally nonadherent	Dichotomous: intentional / unintentional
4) On how many occasions in the past 7 days have you altered the dose of this medication that you took?	Item 4 and 5 (which were used in Pilot B and C) were designed to capture changed doses. These items were also meant to capture overdosing. At this point we were reasoning that changed doses would always be intentional. We later realised that overdosing can be accidental and that these items are capturing incorrect information to calculate adherence rate of overdosing, as well as superfluous information on 'under dosing'. We therefore changed items 4 and 5 so that they capture overdosing according to the same method used in previous items to capture 'under dosing'. (The wording was also changed from 'on how many			
5) When people alter the dose of medication they take, sometimes they take more and at other times they take less. Thinking of doses of				

.....that you have altered in the past 7 days, which of the statements below apply to you? When I altered the dose I took more ☐ When I altered the dose I took less ☐ It depends, on some occasions I took more and on other occasions I took less. ☐	occasions doses have been missed' to 'how much have been missed' as patients may interpret 'dose' differently). These revised items are displayed below. These issues will be discussed further in section 4.3.2.9.

Items taken from DAS-multi	**Construct/s**	**Example answer**	**Example output**	**Range**
6) People often take more of their medicine than has been prescribed. Thinking of the last 7 days: A) How MUCH EXTRA of each medicine did you take in the last 7 DAYS?	Adherence rate	100mg x 2 (2 tablets) of one medicine	Tablets taken = 7+2=9 Adherence rate = ((9/7)x100)= 129%	Continuous: 100%-∞%
7) Here are examples of reasons other people have given taking extra medicine. THINKING OF THE EXTRA DOSES YOU HAVE TAKEN IN THE LAST 7 DAYS, which of the following statements best describe what happened (you can choose more than one option)? A) I decided to take more ☐ B) I accidentally took more ☐ C) Other [Please specify)	Intentional and unintentional nonadherence	P1 ticked 'A' P2 ticked 'B' P3 ticked 'A and B'	P1 is classified intentionally nonadherent P2 is classified unintentionally nonadherent P3 is classified as both intentionally & unintentionally nonadherent	Dichotomous : intentional / unintentional

General comments: during the piloting stages there were two major challenges. Firstly, wording the questionnaire to allow most patients to understand and report their prescribed dose. We initially used the term "dose", but realised this can be interpreted in many different ways. We then changed the wording to use "how much" instead. Secondly, the validity of the items to capture intentional and unintentional nonadherence is an ongoing issue. The current stance is that these items capture enough information to understand the patient's perception of whether the causes are intentional or unintentional. However the patients' perception may not correspond with our definitions. These issues will be discussed further in the piloting sections and discussion sections.

4.3.2 THE PILOTING AND DEVELOPMENT PHASES

Pilot studies are conducted to test the plausibility of research design and methodology in order to inform larger scale studies. Initially, in pilot A, an analysis of whether the last 7 days adherence rate was a valid indicator of overall adherence was conducted on a sample of patients who were monitored using MEMS. Following on from this I will describe the initial version of the DAS-specific, which will be tested and revised in Pilot B (face and construct validity, ease of use and acceptability of DAS-specific) and Pilot C assessed (concurrent validity). Thereafter the DAS-multi will be introduced, which has not yet been piloted.

The three pilot studies were conducted between February 2009 and June 2010.

4.3.2.1 PILOT A METHODS: IS THE LAST 7 DAYS ADHERENCE RATE A VALID INDICATOR OF OVERALL ADHERENCE?

Even though there is existing literature supporting the use of 7 days recall of adherence rate (Haynes et al., 1980, Haynes et al., 2002, Barber et al., 2005, Clifford et al., 2006), some concerns were raised about whether the 7 days preceding an appointment may be different from patients' adherence longer term adherence rates. This is particularly relevant as patients may improve their adherence in the days surrounding a clinical appointment; so called "white-coat" adherence (Feinstein, 1990). Therefore we analysed the adherence rates of patients who were monitored using a MEMS device for three months to see whether the MEMS adherence rate during the final 7 days of the study was significantly different from the patients' longer term adherence rate during the study.

4.3.2.1.1 SAMPLE

The sample consisted of 87 patients with chronic myeloid leukaemia, who had been prescribed imatinib as first line treatment and been on the treatment for 2 years or longer (median 60 months, min-max 25-104 months). The median age was 51 years (min-max 26-89, IQR=34-45) and 56.3% (n=49) of the sample was male. Patients' adherence was monitored with MEMS for a median of 83 (min-max

40 to 120 days). The full details of the trial was introduced in section 2.1 (pp. 90) and have been published elsewhere (Marin et al., 2010).

4.3.2.1.2 PROCESS

The data was analysed in conjunction with a clinical trial at Imperial College London, Hammersmith Hospital. The trial was approved by the Charing Cross medical research ethics committee and participants had given written informed consent. The MEMS data was stored and processed using the computer software PowerView (Aardex Ltd).

The data for this specific analysis was captured by counting the number of times the patient had opened the MEMS bottle directly in the diary view of the program for the respective time periods. Figure 25 below give an example of what such a display looks like. The final day of the trial was excluded as it could not be known whether the openings on that day was the patient opening the bottle (assumed to indicate tablets had been ingested) or the nurse or clinician opening the caps in clinic or when collecting the MEMS caps.

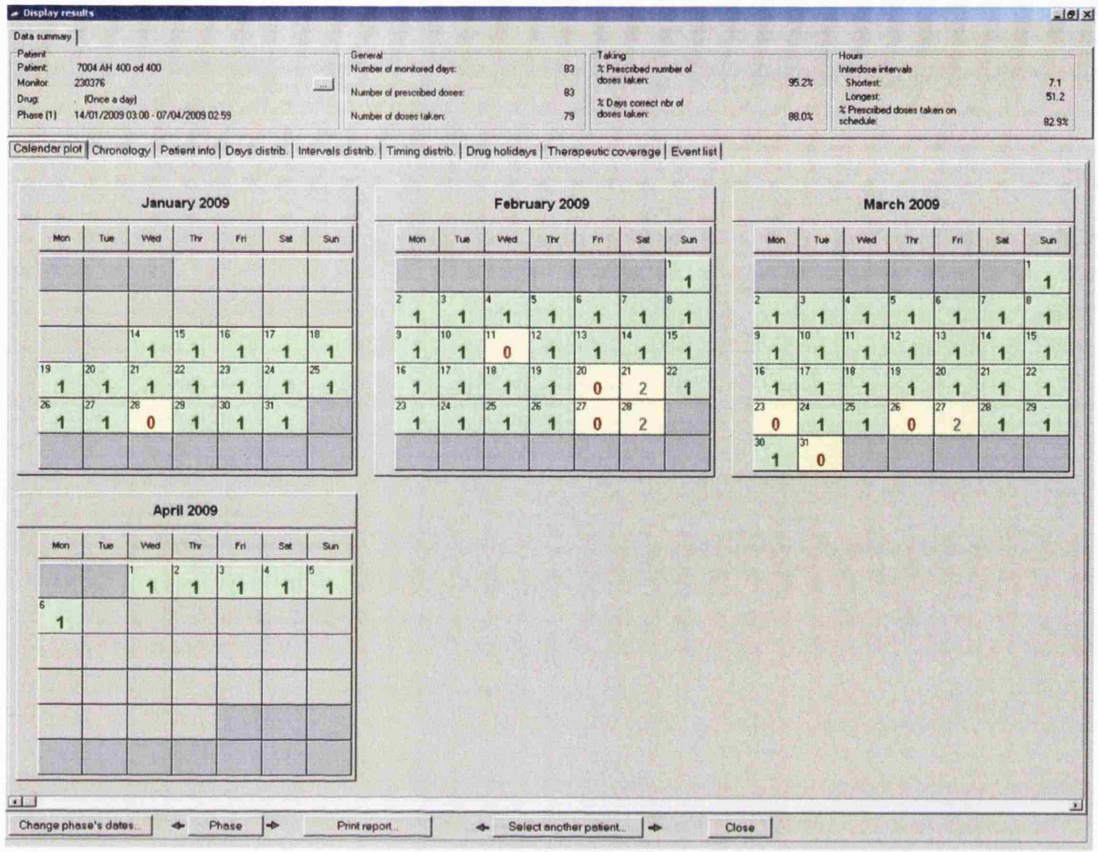

FIGURE 25 DIARY VIEW IN POWERVIEW DISPLAYING A TRIAL PARTICIPANT'S MEMS READING

4.3.2.1.3 ANALYSIS

PASW statistics 18 was used to perform the analysis. It was presumed that the patient had ingested a dose of imatinib each time the MEMS bottle was opened. The patient adherence rates were thus calculated as the percentage of prescribed doses that were ingested as follows:

$$adherence\ rate\ \% = \left(\frac{number\ of\ doses\ ingested}{number\ of\ doses\ prescribed}\right) \times 100.$$

In this way, the mean adherence rate (%) was calculated for the sample for the final 7 days' of the trial, for the 33 days' preceding the final 7 days and for the total trial period excluding the final 7 days (the total number of days in the trial differed between the trial patients) preceding period. Figure 26 shows a visual representation of the different periods included in the analysis.

The reason for excluding the final 7 days from the whole trial period is that the analysis used paired samples t-test to compare the mean adherence rates (%) of the different periods and the periods can thus not overlap. The reason we captured the 33 days preceding the final 7 days of the trial is that we wanted to analyse the mean adherence rate for the same number of days for all patients, and one patient in our sample had only been monitored by MEMS for 40 days in total (40 days excluding final 7 days = 33 days). Paired-samples t-test was used to compare the mean adherence rate during the different time periods within patients. The significance level was set to 0.05.

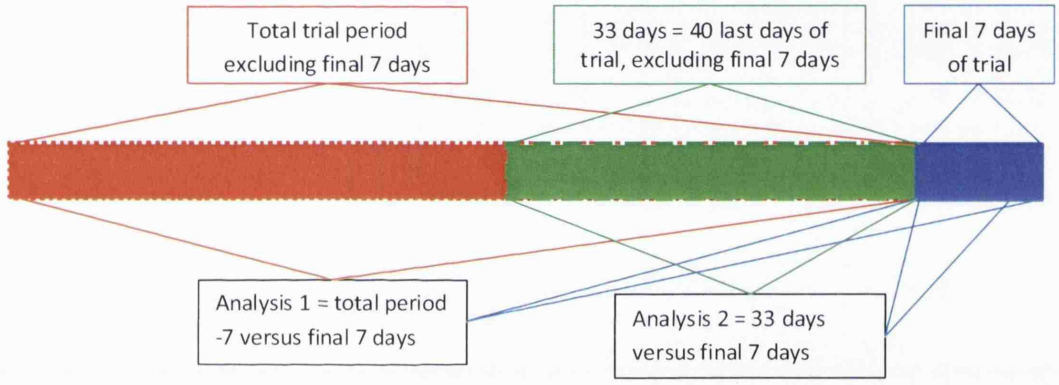

FIGURE 26 VISUAL REPRESENTATION OF THE PERIODS INCLUDED IN THE ANALYSIS OF PILOT A

4.3.2.2 PILOT A RESULTS

Data from 86 of the 87 patients were included in the analysis; one patient was excluded due to missing data.

The mean nonadherence rate (% missed doses) for the final 7 days of the trial was 14% (SD 29), for the 33 days preceding the final 7 days 15% (SD 27) and for the full trial period with the final 7 days excluded 14% (SD 24). The results of the first paired t-test did not detect a difference in the adherence rates of the final 7 days of the trial compared to the total number of monitored days, excluding the final 7 days ($p = 0.22$). Furthermore, the results of the second paired t-test did not detect a significant difference in the nonadherence rates for the final 7 days of the trial

compared to the 33 days preceding the final 7 days (p = 0.43). Consequently, the analysis did not detect a difference between the final 7 days nonadherence rates and the nonadherence rates of either of the longer periods (33 days and the total trial period).

It was therefore concluded that the adherence rate during the final 7 days before an appointment is a valid representation of patients' longer term adherence rates. This supports the validity of using a 7 days recall period to measure self-reported adherence rates, which was used in the DASs scales. The following section will present the early versions of the DAS-specific, which is used to measure patients' self-reported adherence to a single medicine.

4.3.2.3 DEVELOPMENT OF THE DAS-SPECIFIC

This section will present the diagnostic adherence scale that was developed to measure adherence to a single medicine (the DAS-specific) that was tested in pilot B, and then revised before being tested again in Pilot C.

Based on the theory laid out in section 4.3.1, the first version of the diagnostic adherence scale was developed. The strong theory driven development supports the validity of the contents of the DAS-specific. Figure 27 (pp. 250) show the very first version of the DAS-specific that was developed.

This version was tested for face validity by being examined by a psychologist (SC) and a pharmacist (NB) with expertise in the field of medication adherence. This version was then revised according to suggestions. This version was continuously commented on and revised by LE, SG, SC and NB. At this stage the scale was also tested unofficially with friends and colleagues to get informal feedback on ease of use and how clear the questions were to understand. The main changes were clarity of wording, filters directing the patient between questions and highlighted text for important information.

The revised version of the DAS-specific (Figure 28) was tested with patients in Pilot B, section 4.3.2.4 (the instruction to go to question 12 below several of the items in this version of the DAS-specific directs the respondents to audit questions,

which are not displayed here). This version was then revised before Pilot C and these revisions will be discussed in section 4.3.2.6.

1. Are you currently taking _____?
Yes No

If Yes, go to question 2
If No, go to question 8

2. People often miss taking doses of their medicines, for a whole range of reasons. Thinking of _____, when was the last time you missed a dose of this medicine?

Answer:_____
If you have never missed a dose, please go to question 5

3. On how many occasions in the past 7 days have you missed doses of _____?

Answer:_____
If you have not missed any doses in the past 7 days, please go to question 5

4. Below are examples of reasons other people have given for missing doses of their medicines. Thinking of doses of _____ you have missed in the past 7 days, which of the following statements apply to you:

- ☐ I decided it was better not to take it
- ☐ I forgot to take it
- ☐ I was unable to take it
- ☐ Other reason. Please state:

_____

5. People often decide for themselves to alter the dose that they are taking, for a whole range of reasons. Thinking of _____, when was the last time you altered the dose that you took?

Answer:_____
If you have never altered the dose of your medication, please go to question 9

6. On how many occasion in the past 7 days have you altered the dose of _____ that you took?

Answer:_____

If you have not altered your medication in the past 7 days, please go to question 9

7. When people alter the dose of medication they take, sometimes they take more and at other times they take less. Thinking of doses of _____ that you have altered in the past 7 days, which of the statements below apply to you?

- ☐ When I altered the dose I took more.
- ☐ When I altered the dose I took less
- ☐ It depends, on some occasions I took more and on other occasions I took less.

Please continue to question 9

8. Many people stop taking their medicines for a whole range of reasons. Below are examples of reasons other people have given for stop taking their medicines, which of these statements apply to you?

- ☐ I decided it was better to not take it
- ☐ I was unable to take it
- ☐ Other reason. Please state:

_____

FIGURE 27 DAS-SPECIFIC FIRST VERSION

Imperial College Healthcare NHS

NHS Trust

Dear Sir/Madam,

This audit investigates your experience of using prescribed medication. We would be very interested in your views whether or not you are taking it.

We know you may be taking more than one medicine. For the audit, please choose ONLY ONE of the main medicines that you are taking.

This audit is completely voluntary, and if you at any point feel you would like to stop, that's ok. You do not need to tell us why and your care will not be affected.

Thank you very much for taking the time to fill out this audit!

1) What condition are you being treated for?

.....

2) Please name **ONE** of the main medicines which you are taking

.....

3) What is the prescribed dose of.....?

.....

4) Are you currently taking this medication?

Yes ☐
No ☐

If yes go to question 5, if no go to question 11

5) People often miss taking doses of their medicines, for a whole range of reasons. When was the last time you missed taking a dose of.....?

.....

If you have never missed a dose go to question 8

6) On how many occasions in the last seven days have you missed doses of this medication?

.....

[please turn page]

7) Below are examples of reasons other people have given for missing doses of their medicines. Thinking of doses of ..... you have missed in the past 7 days, which of the following statements apply to you?

I decided it was better not to take it ☐
I forgot to take it ☐
I was unable to take it ☐
Other (please specify) .....

8) People often decide for themselves to alter the dose that they are taking, for a whole range of reasons. Thinking of ....., when was the last time you altered the dose that you took?

.....

If you have never altered the dose of your medication go to question 12

9) On how many occasions in the past 7 days have you altered the dose of this medication that you took?

.....

If you have not altered your medication in the past 7 days, go to question 12

10) When people alter the dose of medication they take, sometimes they take more and at other times they take less. Thinking of doses of .....that you have altered in the past 7 days, which of the statements below apply to you?

When I altered the dose I took more ☐
When I altered the dose I took less ☐
It depends, on some occasions I took more and on other occasions I took less. ☐

Please go to question 12

11) Many people stop taking their medicines for a whole range of reasons. Below are examples of reasons other people have given for stop taking their medicines, which of these statements apply to you?

I decided it was better to not take it ☐
I forgot to take it ☐
I was unable to take it ☐
Other (please specify) .....

FIGURE 28 THE VERSION OF DAS-SPECIFIC THAT WAS USED IN PILOT B (QUESTION 12 IS PART OF AN AUDIT THAT IS NOT INCLUDED)

4.3.2.4 PILOT B METHODS: FACE AND CONTENT VALIDITY, EASE OF USE AND ACCEPTABILITY OF DAS-SPECIFIC

4.3.2.4.1 STUDY SETTING

This pilot was conducted in conjunction with a hospital audit, which was approved by Imperial NHS Health Care Trust Governance. The consultants overseeing the patients who were approached at the outpatient clinic gave the approval for us to be present in the clinic waiting room. Because we did not take any blood or biological samples from the patients the Clinical and Investigative Sciences office at Hammersmith Hospital confirmed that the audit did not require written consent before asking the questions. The DAS-specific that was used during pilot B can be seen in Figure 28 on previous page..

4.3.2.4.2 SAMPLE

The sampling strategy was a convenience sample of patients that was approached about participating at a haematology outpatient clinic at Hammersmith hospital. All the patients who attended the outpatient clinic were eligible to be included in the pilot and no exclusion criteria were imposed. Thirty-three patients from the clinic gave verbal consent and were included in the pilot

4.3.2.4.3 PROCESS

Patients were approached in the waiting room of the haematology outpatient clinic and were asked to fill in the DAS-specific questionnaire. The researchers (LE and SG) were present during the time the patients filled in the questionnaires and answered any questions the patients had. Special care was taken to record any difficulties patient had with answering the questions of the DAS-specific.

Content validity of the measure was supported through showing the close link between the theoretical base and the DAS-specific items, as detailed in section 4.3.1.

Face validity was assessed by asking the patients to give verbal feedback on whether the content of the questionnaire appears reasonable and related to the question at hand; in this case medication adherence. Ease of use and acceptability of the questionnaire was assessed qualitatively by the users giving their verbal feedback on these factors. The information was collected by the researcher directly after the patient had filled in the DAS-specific (or if they had questions during filling it in) and was recorded by the researcher directly on the questionnaires. This information was then summarised and is presented in the result section.

4.3.2.4.4 ANALYSIS

Predictive Analytics SoftWare (PASW) 18 was used to support the analysis. Feedback given by patients on face validity, ease of use and acceptability was recorded by the researchers directly on the questionnaires, summarised and used to revise and update the DAS further.

4.3.2.5 PILOT B RESULTS

Thirty-two patients answered the DAS. The mean age was 51 years (range 22-80; SD 15). The patients' illnesses represented in the sample are presented in Table 14 and the treatments the patients had been prescribed in Table 15.

TABLE 14 ILLNESSES REPRESENTED IN SAMLE

Illness	N (%)
Chronic myeloid leukaemia	20 (61)
Lymphoma	3 (9)
Acute Leukaemia	2 (6)
Myeloma	1 (3)
Chronic graft versus host disease	1 (3)
Germ cell tumour	1 (3)
Underactive thyroid	1 (3)
Yolk sac tumour	1 (3)
Renal Failure	1 (3)
Skin condition	1 (3)
TOTAL	32 (100)

TABLE 15 MEDICATIONS REPRESENTED IN SAMPLE

Prescribed medication	N (%)
Imatinib	10 (30)
Dasatinib	5 (15)
Nilotinib	4 (12)
Prednisolone	2 (6)
Steroid	1 (3)
Procarbazine	1 (3)
Omerprazonle	1 (3)
Methotrexate	1 (3)
Morphine	1 (3)
Premique	1 (3)
Magnesium	1 (3)
Thyroxine	1 (3)
Clexine (injection)	1 (3)
Fortisip (nutritional drink)	1 (3)
Periactin	1 (3)
TOTAL	32 (100)

Thirteen percent (n=4) of the patients reported nonadherence; of which, two patients reported intentional nonadherence and 2 patients reported unintentional nonadherence. Face validity was reported by the participants as it was clear that the questions were aimed at finding out how the participants had used their medication in the previous 7 days. The participants took only a few minutes to fill out the DAS questions and very few needed further explanation of the questions. It was therefore concluded that ease of use and acceptability was high in this pilot of the DAS.

4.3.2.6 REVISIONS OF DAS-SPECIFIC

The main issue identified after Pilot B in terms of the scale items was that the DAS-specific captures unnecessary data. For example, question 11 (see below) is not contributing to measuring adherence rate, as a patient who had stopped their medicine would arguably report that they had missed all doses in the last 7 days. Question 11 was therefore excluded from the DAS-specific.

- 11) Many people stop taking their medicines for a whole range of reasons. Below are examples of reasons other people have given for stop taking their medicines, which of these statements apply to you?

- I decided it was better to not take it □
- I forgot to take it □
- I was unable to take it □
- Other (please specify) .....

However, even though questions 5 and 8 in the DAS-specific from Pilot B (Figure 28) may seem superfluous for the purpose of measuring adherence rate, we deemed it important during the piloting phases to know whether patients often reported to have missed doses in the days preceding the 7 days recall period, which would indicate that the 7 days recall period may not be appropriate to capture instances of nonadherence.

- 5) People often decide for themselves to alter the dose that they are taking, for a whole range of reasons. Thinking of ....., when was the last time you altered the dose that you took?
- 8) People often miss taking doses of their medicines, for a whole range of reasons. When was the last time you missed taking a dose of.....?

Imperial College Healthcare NHS

NHS Trust

Dear Patient,

This questionnaire asks about how you are getting on with taking Imatinib (Gleevec). We know that many patients at times miss or change doses of their Imatinib. Some forget, others experience problems that hinder them taking their medicine, and yet other patients adapt their treatment so it better fits in with their life. Please answer the following questions the best you can. The information will help us to understand how we can better support individual patients' treatments to suit their life.

1) People often miss taking doses of their medicines, for a whole range of reasons. Thinking of your Imatinib (Gleevec), when was the last time you missed a dose of this medicine (if never, or you can't remember, then state this)?

.....

2) On how many occasions in the last 7 days have you missed a dose of Imatinib (Gleevec)?

.....

3) Below are examples of reasons other people have given for missing doses of Imatinib (Gleevec). Thinking of the doses you have missed (if any) in the last 7 days, which of the following statements best describes what happened (you can tick more than one box)?

I decided not to take it ☐
I forgot to take it ☐
I was unable to take it (for practical reasons) ☐
I did not miss any doses ☐
Other (please specify).....

4) People often decide for themselves to change the Imatinib (Gleevec) dose that they are taking, for a whole range of reasons. Sometimes they take more and at other times they take less than the prescribed amount. When, if ever, was the last time you altered the dose of Imatinib that you took?

.....

5) On how many occasions in the past 7 days have you changed the dose of Imatinib (Gleevec)?

.....

6) Thinking of doses of Imatinib (Gleevec) that you have changed in the past 7 days, if any, which of the following statements apply to you?

When I changed the dose I took more ☐
When I changed the dose I took less ☐
It depends, on some occasions I took more and on other occasions I took less ☐
I did not change any doses ☐

PILOT C DAS-IMATINIB-v1(240209).doc END OF QUESTIONNAIRE

Office use only
M/F Age:____
Ad
IntNonAd
UnNonAd

FIGURE 29 THE VERSION OF DAS-SPECIFIC USED IN PILOT C

4.3.2.7 PILOT C METHODS: CONCURRENT CRITERION VALIDITY, SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES OF DAS-SPECIFIC

Pilot C tested concurrent criterion validity, sensitivity, specificity and predictive values of the DAS-specific.

Figure 29 display the DAS-specific as it was used in Pilot C. We also tried to compress the DAS-specific by stripping some general questions about treatment that were deemed unnecessary, and because the questionnaire now only included 6 questions we excluded the filters directing patients to different questions to reduce the text. This was meant to make the questionnaire more concise to use. In addition, because this version of the DAS-specific was tested in patients who took imatinib for CML only, we pre-printed the medication name to make the scale easier to use.

4.3.2.7.1 SAMPLE

Eighteen patients with chronic myeloid leukaemia, who had been prescribed imatinib as first line treatment, were included in the pilot study. The sample was a convenience sample. The inclusion criterion was that the patient had participated in the clinical trial, there was no exclusion criteria imposed. The median age was 47 years (range 32-62, IQR 39-58) and 65% (n=11) of the sample was female. The patients' adherence rates had been monitored using MEMS and their MEMS data for the final 7 days preceding the appointment was included in the analysis.

4.3.2.7.2 PROCESS

Data was collected between February and May 2009. The pilot was conducted in conjunction with a clinical trial at Imperial College London, Hammersmith Hospital. The trial was approved by the medical research ethics committee and participants had given written informed consent. The patient gave verbal consent to be included in the pilot study.

Pilot C tested the concurrent validity of 7 days recall self-reported adherence rate as measured by the DAS-specific (Figure 29) and 7 days MEMS reading from the same period.

Patients were asked by the senior clinical trial nurse at the end of their trial appointment whether they would like to participate in a pilot study testing a short questionnaire. If the patient gave verbal consent to the nurse that they were happy to participate they were given an information sheet stating their answers are anonymous, that the answers will only be linked to their results through the trial number and that only researchers from the School of Pharmacy will be able to see their responses. All patients were given an envelope to seal their responses into and the trial nurse then put their trial number on the outside of the envelope so that their answers could be related to the trial MEMS readings.

The MEMS data was collected by directly accessing the diary view of the MEMS recordings through PowerView (Aardex Ltd) and counting the number of openings during the previous 7 days, assuming that each opening of the bottle correspond to the patient ingesting an imatinib tablet. Figure 25 (pp. 246) displays one patients' diary view of the MEMS reading. The day of the appointment was excluded when counting the openings as it could not be determined whether it was the patients who had opened and ingested medication or if it was opened by health care providers (HCPs) as they collected the MEMS devices.

4.3.2.7.3 ANALYSIS

Analysis of the DAS questionnaires was performed and compared to the patients' MEMS reading for the final 7 days (using the PowerView diary view, as displayed in Figure 25). The data was captured and entered into an excel spreadsheet, including patient self report of missed or changed doses and MEMS reading. In addition, any further information, such as when the patient last missed a dose and written notes patients had left on the DAS was captured and compared to readings from the MEMS.

The 7 days MEMS adherence rates were calculated as

$$\left(\frac{number\ of\ openings}{number\ of\ doses\ prescribed}\right) \times 100,$$

and could range from 0% to >100%. Self-reported adherence rate was calculated as

$$\left(\frac{number\ of\ doses\ taken}{number\ of\ doses\ prescribed}\right) \times 100,$$

and could range from 0% to >100%. A paired samples t-test was performed to explore differences between the means of the DAS adherence rates (%) and the MEMS adherence rates (%). However, this is a pilot study with a small sample size, which means the study is not powered to detect a difference in adherence rates even if a significant difference existed, thus the two analyses are only done to explore the data. PASW statistics 18 was used to perform the analysis.

The sensitivity and specificity, as well as the positive and negative predictive values, were calculated for the DAS using the 7 days MEMS reading as "gold standard". These values were calculated according to the simple formulas displayed in Table 16. In order to calculate these values, the patient has to be dichotomised into adherent or nonadherent according to a cut-off point. This is because all of these values are ways to determine the prognostic qualities of a measure, i.e. whether the measure can correctly diagnose patients.

For CML patients taking imatinib, the cut-off point for adherence rate below which it is likely to have an impact on clinical outcome is 90%. Patients were prescribed either 7 or 14 doses of imatinib per week. We therefore decided to use one missed dose of 7 as cut-off point to dichotomise adherent and nonadherent patients. One missed dose per week give an adherence rate of ((6/7)x100)=86%. Consequently, with an adherence rate >86% were considered adherent and patients with an adherence rate ≤86% were considered nonadherent.

TABLE 16 FORMULA TO CALCULATE SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES

		MEMS		
		Nonadherent	Adherent	
DAS	Nonadherent	True Positive (TP)	False Positive(FP)	Positive predictive value = TP / (TP + FP)
	Adherent	False Negative (FN)	True Negative (TN)	Negative predictive value = TN / (FN + TN)
		Sensitivity = TP / (TP + FN)	Specificity = TN / (TN +FP)	

4.3.2.8 PILOT C RESULTS

Data from seventeen patients were included in the analysis in which two methods of assessing adherence were compared (the DAS-specific was compared with the MEMS data). One patient was excluded as their MEMS data was missing.

The analysis revealed that there were no discrepancies between the DAS and MEMS in 8/17 cases, of which 7 reported to not have missed doses in last 7 days (i.e. adherent) and one patient reported to have missed 1 dose (i.e. nonadherent). In addition, in 1/17 case where there was a discrepancy between DAS and MEMS the patient reported to have missed 2 doses in last 7 days, but only one was recorded by MEMS. This patient would thus have been classified as nonadherent by both measurement methods although the adherence rate would have differed.

In the remaining 8/17 cases there were discrepancies between DAS and MEMS. In each of these cases, participants reported via the DAS that they had not missed doses in the last 7 days; however, missed doses in this period were recorded by MEMS. As previously stated, the MEMS assessment works on the assumption that the patient does ingest an imatinib tablet each time an opening of the bottle is recorded.

Nevertheless, only one of these patients, presumed to have missed doses in the last 7 days based on MEMS readings, stated in the DAS to never have missed a dose. Of the remaining patients, 2 stated to not remember when they last forgot and one

patient stated they "sometimes forget" their afternoon dose. The remaining 4 all stated that they had missed a dose/doses recently, but not within the last 7 days.

The mean adherence rate according to the DAS was 97% (SD 22) and according to the MEMS 87% (SD 8). Using a paired samples t-test, this difference was not statistically significant (p = 0.07). However, this analysis was done purely to explore the relationship of the two means as the sample size is too small to detect a significant difference even if a true difference exists. From just looking descriptively at the difference in mean adherence rates from the two measures, it suggests that the DAS underestimates adherence compared to the MEMS, assuming that the MEMS is generally a more accurate measure of "true" adherence than the DAS.

Table 17 shows the results for the sensitivity, specificity, positive predictive values and negative predictive values of the DAS, using MEMS as the "gold standard". The results show that the sensitivity was very low (0.25), which means many patients who were nonadherent according to 7 days MEMS readings were not identified as nonadherent by the DAS. On the other hand, specificity was perfect, which indicate that all the patients who were identified as adherent according to the MEMS reading were also identified as adherent according to the DAS. The positive predictive value was also perfect, which means that all patients who scored as nonadherent were correctly identified as nonadherent. The negative predictive value was 0.6, which mean that many patients who scored as adherent were incorrectly identified as adherent by the DAS (as compared to MEMS).

TABLE 17 RESULTS: SENSITIVITY, SPECIFICITY AND PREDICITVE VALUES OF DAS-SPECIFIC AGAINST 7 DAYS MEMS ADHERENCE RATE

		MEMS		
		Nonadherent	Adherent	
DAS	Nonadherent	True Positive (TP) = 2	False Positive(FP) = 0	Positive predictive value = TP / (TP + FP) = 1
	Adherent	False Negative (FN) = 6	True Negative (TN) = 9	Negative predictive value = TN / (FN + TN = 0.6
		Sensitivity = TP / (TP + FN) = 0.25	Specificity = TN / (TN +FP) = 1	

In summary, this pilot study has given us some initial data on the concurrent validity and diagnostic ability of the DAS. This sample size did not have enough power to detect a difference between the adherence rates assessed by the two measure, even if one existed. Therefore, the next step is to test concurrent validity in a larger sample with enough power to detect a difference and this pilot will inform the sample size calculations for the full scale study. The sensitivity of the DAS was found to be very low, which means that many patients who were nonadherent according to MEMS reported that they were adherent on the DAS. However, further testing in a larger sample is needed to draw any conclusions.

4.3.2.9 GENERAL ISSUES IDENTIFIED AFTER PILOT B AND C REGARDING SCALE ITEMS THAT WERE REVISED IN SUBSEQUENT VERSIONS OF THE DIAGNOSTIC ADHERENCE SCALES

There were two important issues that were identified after Pilot B and C with the items of the DAS-specific. Firstly, items 9, 10 and 11 of DAS-specific Pilot B (Figure 28, pp. 251) and items 4, 5 and 6 of DAS-specific Pilot C (Figure 29, pp. 256) were deemed inappropriate. These items were meant to capture overdosing and we initially reasoned that changed doses would always be intentional. However, we later realised that overdosing could be accidental. In addition, these items were capturing incorrect information to calculate adherence rate due to overdosing. Finally, we reasoned that we do not need to capture additional information about whether people altered the dose and took less than prescribed, as this information has already been captured by asking the patients if they have missed doses.

Consequently, these items were exchanged for an item simply asking 'how many extra doses' have been taken in the last 7 days. In addition, to capture whether these extra doses were taken intentionally or unintentionally an item was included where the patient was asked to tick one or more of the following (these two items are included in DAS-multi, which is displayed in Figure 30 in the following section):

A) I decided to take more □

B) I accidentally took more □

C) Other (please specify) .....

Secondly, patients may interpret 'dose' in a range of different ways or get confused. To avoid misunderstandings this wording was therefore changed to 'how much' in subsequent versions of the DAS.[2]

4.3.2.9 DEVELOPMENT OF DAS-MULTI

The DAS-multi was developed to measure adherence rates to multiple medicines. In the setting where the DAS-multi is to be piloted it will be more suitable to use a structured interview guide DAS that can be used to assess patient adherence rates over the phone[3]. In addition, a structured interview guide may be more appropriate for use in clinical practice by clinicians or other HCPs to assess adherence rates. The version of the DAS-multi that was developed is shown in Figure 30 (pp. 265).

The DAS-multi was developed according to the theoretical basis described in section 4.3.1 (pp. 237) and included the revisions that have been mentioned in the previous section. The DAS-multi interview schedule has a major difference compared to the DAS-specific in that it includes a response sheet where all the patients' responses are recorded on a single spread sheet. This can be seen in Figure 31 (pp. 266).

Item 1 of the DAS-multi asks the patient for the names and dosage of the medicine that has been prescribed. However, it was reasoned that some patients may find it difficult to remember multiple medication names. Therefore, an item was added where patients were asked simply about the number and formulation of medicines s/he has been asked to take. This way it is still possible to calculate the patients'

---

[2] The exception is medication specific scales that are under development, where the DAS can be adapted to ask directly for the formulation of the prescribed medication, e.g. how many tablets of imatinib have you been prescribed/how many tablets of imatinib have you missed.

[3] One of the main reasons for this was that we are currently developing this measure is to support future validation study of a adherence service provided by a primary care trust, and the methods we will use for this study is phone based patient interviews.

adherence rate, even though specific medication names cannot be remembered by the patient.

DAS-multi|Pilot D

These questions ask about how you are getting on with taking your medicines. We know that many patients at times miss or change doses of their medicines. Some forget, others have various problems taking their medicine, and yet other patients adapt their treatment so it better fits in with their life. Please answer the following questions the best you can. The information will help us to understand how we can better adjust individual patients' treatments to suit their life.

1) Thinking of the medicines your doctor has prescribed:

A) WHICH medicines have you been asked to take?

B) HOW MUCH of these MEDICINES have you been asked to take each DAY?

Record answers on response sheet: DAS page 3 – question 1A and question 1B

If patient is able to answer go to question 3
If s/he is NOT sure go to question 2

2 Thinking of the medicine your doctor has prescribed:

A) How many tablets and capsules have you been asked to take each day?

B) How many spoonfuls of medicine have you been asked to take each day?

C) How many puffs of inhalers have you been asked to take each day?

D) How many creams have you been asked to use each day?

E) How many injections have you been asked to have each day?

F) Have you been asked to use any other type of medication?

If so how much?

Record answers on response sheet: DAS page 3 – question 2

3) People often miss taking doses of their medicines, for a whole range of reasons. Thinking of the last 7 days:

A) HOW MUCH of each medicine have you MISSED taking in the last 7 DAYS?

Record answers on response sheet: DAS page 3 – question 3

If patient has NOT missed any, GO TO question 5

4) Here are examples of reasons other people have given for missing medicines. THINKING OF THE MEDICINE YOU MISSED IN THE LAST 7 DAYS, which of the following statements best describe what happened (you can choose more than one option)?

A) I decided not to take it ☐

B) I forgot to take it ☐

C) I was unable to take it ☐

D) Other (please specify) .....

5) People often take more of their medicine than has been prescribed. Thinking of the last 7 days:

A) How MUCH EXTRA of each medicine did you take in the last 7 DAYS?

Record answers on response sheet: DAS page 2 – question 5

If patient has taken extra GO TO Question 6

6) Here are examples of reasons other people have given taking extra medicine. THINKING OF THE EXTRA MEDICINE YOU HAVE TAKEN IN THE LAST 7 DAYS, which of the following statements best describe what happened (you can choose more than one option)?

A) I decided to take more ☐

B) I accidentally took more ☐

C) Other (please specify) .....

Page 3: Response sheet for DAS questions 1A, 1B, 2, 3A and 5A

FIGURE 30 THE VERSION OF DAS-MULTI THAT WAS TESTED IN PILOT D

Question 1A	*Question 2*	*Question 1B/2*	*Question 3*	*Question 5*
Name of medicine	**Dosage form**	**Dose (How much)**	**Amount MISSED in last 7 DAYS**	**Amount EXTRA in last 7 DAYS**
Med 1	**Tablets/capsules**			
Med 2	**Liquids**			
Med 3	**Inhalers**			
Med 4	**Creams**			
Med 5	**Injections**			
Med 6	**Other**			
Med 7	**Other**			
Med 8	**Other**			
Med 9	**Other**			
Med 10	**Other**			

NB Fill in either question 1A or Question 2

FIGURE 31 SCORE SHEET FOR DAS-MULTI

4.4 DISCUSSION

This chapter presented three pilot studies conducted during the development of two versions of a new self-report adherence scale; the diagnostic adherence scale for measuring adherence rate to a single medicine (DAS-specific) and the diagnostic adherence scale for measuring adherence rates to multiple medicines (DAS-multi). The reason two scales were developed instead of just one for multiple medicines, which then naturally could be used to measure the adherence rate to a

single medicine as well, was to keep the DAS-specific as simple as possible for monitoring of a single medicine only.

Pilot A tested whether the 7 day recall period is a valid representation of longer term adherence rates. Results did not show a significant difference in adherence rates between the 7 days preceding a clinical appointment and longer term adherence rates. This implies that 7 days may be representative of patient adherence rates overall and supports the validity of using a 7 days recall period for patients to report doses missed or taken extra. Pilot B supported sufficient face and content validity of the DAS-specific, and concluded that ease of use and acceptability of the DAS-specific appeared high. Pilot C tested the concurrent validity, sensitivity, specificity and predictive values of the DAS-specific compared to 7 days MEMS reading. There were many discrepancies between the DAS-specific reports and the MEMS readings, which raises many questions regarding the best method of assessing criterion validity of the DASs. In particular, it is unclear what the best criterion is for assessing adherence measures against, as there is arguably no "gold standard" of adherence measurement. Possible methods will be discussed in section 4.4.2. The sensitivity in this small sample was very low (0.25) indicating that many patients who were diagnosed as adherent according to the DAS-specific were classified as nonadherent according to MEMS. However, all the patients who were adherent according to MEMS were also adherent according to the DAS-specific, indicating high specificity.

4.4.1 STRENGTHS AND LIMITATIONS OF THE DAS

The most important strengths of the two diagnostic adherence scales (DASs) compared to other adherence measurements are that they measure adherence rate on a continuous scale and capture whether detected nonadherence is due to intentional or unintentional causes (or both). That the DASs provide continuous scale outcome data means that the DASs would be suitable to measure change adherence rates over time. This is in contrast to most other self-report adherence measures, which are generally categorical (e.g. Morisky et al., 1986, Morisky et al., 2008, Krousel-Wood et al., 2009, Haynes et al., 1980, Gehi et al., 2007), although exceptions exist (Svarstad et al., 1999, Giordano et al., 2004, Walsh et al., 2002). Continuous scale data is particularly suitable to be used when taking a system approach to work towards solutions to facilitate patients' adherence to prescribed treatments, such as supporting continuous quality improvement processes implemented in primary care systems.

Another advantage with continuous scale outcome data is that the scale can also be used as a categorical measure dichotomising patients into adherent or nonadherent groups according to a pre-defined (and scientifically supported) cut-off point. This is useful, for example, if patients are going to be allocated to different support groups depending on if they have problems with adherence or not.

Furthermore, in difference to most other adherence measures the DASs seems to differentiate between intentional and unintentional nonadherence. This is an important characteristic for a scale that is to be used in clinical practice as intentional and unintentional nonadherence have different causes and therefore require different solutions (Nunes et al., 2009, WHO, 2003, Horne et al., 2005). To be able to capture whether the patient was intentionally or unintentionally nonadherent is one of the key differences between the DAS and many other self report measures, such as the four item Morisky scale (Morisky et al., 1986) and the visual analogue scale (Giordano et al., 2004).

The four item Morisky adherence scale (Morisky 1986) has recently been updated to an 8 item scale and validated in hypertension (Morisky 2008). Each item of the 8 item scale measures a specific medication taking behaviour, for example 3 items ask about forgetting and one item asking the patient about whether they "feel hassled about sticking to your blood pressure treatment plan". Response categories are yes/no for 7 items, which require a dichotomous response. The final item ("How often do you have difficulty remembering to take all your blood pressure medication?") uses a 5-point Likert response. Patients scoring 8 on the 8 item scale are classified as having high adherence, 6-7 as having medium adherence and 0-5 as having low adherence. In difference to the DASs the Morisky 8 item is a measure that classifies patients according to the presence or absence of certain behaviours. This means the 8 item Morisky does not produce a continuous adherence rate, in the way that the DASs does. The DASs produces an adherence rate as a percentage; the number of doses taken from the number of doses that have been prescribed. In addition, the 8 item Morisky scale does not dichotomise respondents according to whether their nonadherence is due to intentional or unintentional causes; although it does ask about both intentional and unintentional behaviours the dichotomy is not specifically addressed in the paper (Morisky 2008). Consequently, the 8 item Morisky may be useful to identify nonadherent patients, but cannot be used to direct appropriate interventions to address the intentional or unintentional causes of the patients' nonadherence.

Nonetheless, a limitation highlighted in the pilots was that the sensitivity of the DAS-specific was found to be very low (0.25), which means that many patients who were nonadherent according to MEMS reported that they were adherent on the DAS-specific. Even though further testing in a larger sample is needed to draw any conclusions on the diagnostic sensitivity of the DASs, this finding is in line with the general limitation of self-report measures to underestimate nonadherence due to social desirability and recall bias (Nunes et al., 2009). However, how the DASs scales have been designed to minimise these biases have already been discussed in the development section 4.3.1 (pp. 237). Briefly, social desirability bias is meant to be reduced by framing the questions in a non-judgemental way and presenting nonadherence as a normative behaviour; whereas recall bias was meant to be reduced by limiting the recall period to 7 days.

However, there are also general strengths that the both the DAS-specific and the DAS-multi would share with other self-report measures. For example, affordability, ease of administration and comparably nonintrusive of self-report measures are great advantages compared to other more intrusive measures such as MEMS, which are very expensive and pill-count, which are cumbersome to perform for the health care provider. Affordability and ease of administration are particularly important if the measure is to be used for continuous monitoring of adherence rates in organisations that are usually constrained by strict budgets and limited resources, such as the NHS.

4.4.2 FURTHER DEVELOPMENTS OF THE DAS

This section will outline the validation assessments that should be performed before the DAS-specific and the DAS-multi can be recommended (or not recommended) for wider use to measure and monitor adherence to medication.

As discussed previously, reliability is the most basic criteria for the evaluation of a measure, as a test that is unreliable cannot be valid either. Test-retest reliability of the DASs has to be conducted with little time difference, as a difference in reported adherence rate may correspond to a real change in adherence rate over time. Ideally, participants' should be measured on the same day. Test-retest reliability was not evaluated in these pilots, and should be performed in future studies of the DAS.

Inter-rater reliability, the evaluation of whether two different assessors would score the same participant identically, is only relevant to the DAS-multi, where the measure is used as a structured interview schedule. Again this evaluation should ideally be done on the same day as a difference in adherence rate may constitute a real difference.

Face and content validity should be reassessed in relation to the final version of the DAS-specific and DAS-multi before they are published. Full content validity, in particular, needs to be established through systematic examination of the measurement content by professionals who have experience in the adherence field, but who have not been involved during the development and piloting phases.

Construct validity of the items that dichotomise intentional and unintentional adherence should be assessed. Convergent construct validity of intentional nonadherence could be assessed against patients' beliefs about the necessity of taking their medicines and the related concerns for taking their medicines, which has been shown to be associated with intentional nonadherence (e.g. Clifford et al 2008; Horne 1999). Unfortunately, there has so far not been discovered any similar associations for unintentional nonadherence, but it is possible measures of memory difficulties or problems with dexterity will be associated with unintentional nonadherence.

Predictive criterion validity has not been piloted for the DAS. It would, however, be desirable to test the predictive validity of the DAS in future validation studies. One method would be to correlate the DAS scores with future clinical outcome. In particular in illnesses where adherence has been shown to be associated with clinical outcome, in the way as, for example, imatinib adherence in related to clinical outcome in CML patients (Marin et al. 2010; Noens et al. 2009).

Concurrent criterion validity was piloted for the DAS-specific against MEMS in pilot C. However, there is a possible problem with validating self-report of doses missed or taken extra during exactly 7 days against such a precise measure as the MEMS; namely, the patient's recall is likely to be less precise than the MEMS reading. For example, if a patient missed one dose on the 8th day counted backwards from the assessment day, how likely is that patient to state that a dose was missed in the last 7 days? Correct recall is probably increased if linked to a particular event, and intentional nonadherence is probably more likely to be remembered correctly compared to unintentional nonadherence, as attention has been given to make the decision of missing a dose. MEMS recordings, on the other hand would always be accurate recordings of days the bottle was opened or not (although based on the assumption that bottle openings equates to ingested doses). Nonetheless, it would also be difficult to validate the DAS against another 7 days recall measure as the participant is likely to give identical answers to the questions if s/he understands the answers are expected to be identical.

The validation assessments discussed in this section will be conducted to further evaluate the DAS-specific and the DAS-multi for measuring adherence to medication. The following section will briefly introduce one pilot and one larger scale study that have been submitted to medical research ethics committees and if approved will be conducted/initiated in late 2010 or 2011.

4.4.3 UPCOMING VALIDATION STUDIES

We are currently awaiting ethics approval for two studies evaluating the two diagnostic adherence scales. One study is a pilot for the DAS-multi for primary care aiming to recruit 20 patients. This pilot includes administering the DAS-multi to patients attending GP surgeries at a local hospital as well as accessing these patient's medical records in order to obtain a list of the name and dosage of medication which has been prescribed. This will enable the researcher to use the DAS to obtain an adherence rate and will also help inform future use of the DAS by determining how easy it was for patients to remember their medication accurately. This pilot will also assess qualitatively the acceptability, face and content validity of the DAS. For example, verifying the statement meant to dichotomise intentional and unintentional nonadherence by asking patients who stated they were unable to take a dose, why they were unable to take it?

We are also currently in the process of attaining ethics approval for a clinical trial that will be investigating the effect of adherence to nilotinib therapy on response in newly diagnosed CML patients (led by Dr David Marin at Imperial College London and funded by Novartis). We will validate the DAS-specific in conjunction with this trial. Patients' adherence will be assessed prospectively for 12 months using MEMS from the date of initiating nilotinib treatment at diagnosis, with a further 12 months follow-up, making the total follow-up period 24 months. The patients will be asked to answer a battery of questionnaires at the 6 and 12 months follow-up appointments, including the DAS-specific, a visual analogue scale (VAS) that has previously been validated to measure adherence rates in HIV/aids patients on HAART (Giordano et al., 2004) and BMQ (Horne et al., 1999), which has been shown to be related to intentional nonadherence (e.g. Clifford et al., 2008). Concurrent criterion validity for the adherence rates (with no discrimination

between intentional and unintentional nonadherence) will thus be tested against MEMS and the VAS. Predictive criterion validity can also be assessed using clinical outcome as criterion to see whether nonadherence reported on the DAS predict clinical response to nilotinib. In addition, construct validity of intentional nonadherence will be tested against the BMQ. Sensitivity, specificity and predictive values will also be assessed against MEMS in this study.

4.4.4 IMPLICATIONS FOR PRACTICE

As discussed in 4.1.2, as well as the introduction chapter of this thesis, current policy has identified reducing treatment nonadherence as a priority for the health care system (Nunes et al., 2009, Horne et al., 2005, WHO, 2003). This priority is based on evidence of widespread nonadherence, which has significant impact on health. As people are increasingly living longer, the older population is growing and increased prevalence of chronic conditions that require self-administered medication the problem of nonadherence is likely to be on the increase. Having reliable and valid measures are essential to research when evaluating adherence interventions and in practice to support continuous improvement initiatives. Thus far no adherence measurement has been validated that can be recommended for wider use in the NHS to support such evaluations.

The two diagnostic adherence scales (DASs) were developed to provide an easily administered, inexpensive and valid measure of adherence that can be used in both research and practice. The DASs were developed in accordance with taking a system perspective and provides a continuous scale outcome measure, which is the ideal outcome data in measuring change in adherence rates over time. The system approach promotes openness in reporting instances of nonadherence instead of judging the patients less able to adhere and focuses on finding solutions to improve the whole system that may influence patients' capacity to adhere (although, a patients' choice to not adhere should also be respected, with few exceptions).

In order to allocate patients to the appropriate interventions to address nonadherence, understanding patients' reasons for why they miss doses is

essential. The most important distinction is made based on whether the patient's reasons for not adhering are intentional or unintentional. Few existing adherence measures can make this distinction. The DASs, on the other hand, have been developed with this particular dichotomy as one of the distinguished features. This is likely to prove a great advantage compared other measures, should future validation studies provide evidence for recommending the DAS-specific and the DAS-multi for wider implementation.

4.4.5 CONCLUSION

This chapter has presented three pilots of the newly developed adherence measurement DAS-specific and discussed the possible advantages of the measure over other existing adherence measures. Pilot studies are only meant to highlight areas of the measurement and research methods that can be improved before a larger scale study is conducted. In essence the pilots have implied that the DASs may prove to be valid and easily administered adherence measurements that will be useful for future research and practice. However, further validation is needed before it can be recommended for wider use. The final chapter 5 will conclude this thesis by discussing the relations between adherence behaviour, theory and measurement and the new knowledge this thesis has contributed to these areas.

Chapter 5: Discussion

The research presented in this thesis has contributed knowledge and critical thinking that has advanced our understanding of cancer patients' medication taking behaviours, as well as related theories and measurements. The thesis aimed to widen the focus from understanding nonadherence from a person centred view that is focused on changing individual patients' behaviour to a system view that is focused on identifying the underlying causes when working towards solutions. This is in line with recently published UK health policy documents that promote supporting patient adherence to treatment, improved cancer care and a safer use of drug (Nunes et al., 2009, DoH, 2008, DoH, 2010, DoH, 2007). In addition, the system perspective may have a wider application in explaining nonadherence as a medication error in other illness and treatment groups. In essence, this thesis has laid the ground work to further research into understanding nonadherence as a medication error by adapting the Accident Causation Framework (ACF; Reason 1990; 2001) to explain nonadherence and by developing a self-report measure that can be used to monitor adherence rates.

The paradigm for investigation of oral anticancer drugs for this thesis was CML patients prescribed imatinib. The reason for focusing on imatinib was that imatinib has in essence transformed CML from an often terminal illness to a chronic disease that can be managed by patients at home, which means treatment success relies on the patients' ability and motivation to adhere. In addition, at the time of initiating this research no previous studies had been published that investigated adherence to imatinib. Nonetheless, during the course of this research two studies have been published, in addition to our UK clinical trial, which suggest that nonadherence to imatinib is common, has adverse clinical consequences and may increase health care costs (Marin et al., 2010, Noens et al., 2009, Darkow et al., 2007).

5.1 KEY ORIGINAL CONTRIBUTIONS OF THE THESIS

One of the key contributions of this thesis is knowledge of chronic myeloid leukaemia patients' reasons for missing doses of imatinib, which is the first line treatment for CML in the UK. It is essential to understand why patients miss doses in order to develop ways to help patients adhere optimally. In addition, a somewhat unexpected finding was that patients did not seem to appreciate the dangers of missing relatively few doses (i.e. 3 or more doses per month). Many patients reported having been reassured in this belief through clinical feedback and information provided by health care professionals involved in their care.

The thesis also presented an original analysis of different patterns of nonadherence by comparing patients' experiences with using imatinib with the pictorial data output of the MEMS. The analysis particularly highlighted the limitations of using MEMS in trials, both from the point of interpreting the data without take account of the background stories for apparent missed doses and from the point of the influence the MEMS had on some patients ability to adhere as normal (e.g. as patients were not able to use adherence aids such as Dosette boxes).

The thesis also for the first time presented a version of the accident causation framework (Reason 1990) adapted specifically to nonadherence. In particular, the previously emotive language of error and accidents has been adapted to be more appropriate for discussing patients' behaviour. In addition, a feedback loop within the system has been made explicit in the model to highlight the need for appropriate feedback and monitoring of nonadherence to support future adherence enhancing interventions.

5.2 MAIN FINDINGS OF THE THESIS

5.2.1 CHRONIC MYELOID LEUKAEMIA PATIENTS' MEDICATION TAKING BEHAVIOURS

Chronic myeloid leukaemia patients' reasons for not taking the oral anticancer drug imatinib as prescribed has been captured for the first time through the in-depth interviews presented in chapter 2 and chapter 3. In line with previous knowledge the patients expressed both intentional and unintentional reasons for not adhering as prescribed (Nunes et al., 2009, Horne et al., 2005, WHO, 2003).

The most common reason for choosing to not take the imatinib in this group of patients was directly or indirectly to deal with adverse effects of the drug. This included reducing ongoing side-effects, stopping during times of falling ill or travelling, not taking the drug if food is not available and not taking the drug when drinking alcohol. These reasons are similar to why patients from other illness groups are missing doses or modifying their regimen, in particular patients on drugs such as HAART for HIV that often experience severe side effects (Pound et al., 2005). Side effects were also found to be associated with imatinib nonadherence in the clinical trial (Marin et al.) and have been found to be associated with treatment discontinuation in breast cancer patients taking tamoxifen (Lash et al., 2006).

Unintentional reasons for nonadherence could be divided into two main groups: internal and external reasons. The most commonly stated internal reason was forgetting but also included physiological constraints which make it difficult to take the tablets. The external reasons included the pharmacy not having imatinib available to dispense and not having been prescribed enough imatinib to last until the following appointment. That patients at times forget to take doses and that physical barriers can cause nonadherence has been known (Bosworth, 2006, Horne et al., 2005). However, system levels factors such as limited supply of imatinib or prescription errors are rarely analysed in terms of impact on patient adherence in UK settings.

Moreover, the issue of "safe-foods" to reduce side-effects was brought up in the interviews, as well as during the feedback session held for patients. In addition, other patients mentioned that taking imatinib with food acted as a prompt to remind them about taking the imatinib. This suggests that taking imatinib with food supports adherence in two ways, both by reducing side effects and by reminding the patient to take the imatinib. In line with this, the clinical trial results also showed that patients who took their imatinib with food were more likely to be adherent (Marin et al., 2010).

Nonetheless, considering that CML is an inexorable fatal disease if left untreated, an unexpected finding from these interviews was the patients' did not think missing "the odd dose" would matter. In fact, it seemed this belief had been reinforced by feedback they had received from health care providers (HCPs) as well as individual patients' experience of having had treatment interruptions. At the same time, it was clear that many patients relied on their clinician to let them know if their nonadherence had adverse effect on their clinical response, although patients would rarely discuss their nonadherence in clinic.

It was clear that nonadherence changed over time, a finding that has not got much attention in the literature before, with a trend of patients reporting increased intentional nonadherence and a decrease in unintentional nonadherence over time. This trend seemed to be because patients found strategies to deal with the unintentional causes of nonadherence with experience. For example, by creating routines and prompts to facilitate adherence, as well as using conventional adherence aids such as alarms and monitored dosing boxes. The increased intentional nonadherence seemed to be prompted by perceiving the treatment as working through getting positive clinical feedback and therefore becoming less concerned with upholding strict adherence.

The exploration of patterns of nonadherence showed 6 distinct patterns emerge. The adherent patients were generally found to take their imatinib in an organised and timely manner over the trial period. In contrast, the most common pattern of nonadherence was to apparently 'randomly' (frequently or occasionally) miss doses. These patients' adherence rates did not seem affected by the two

appointments at the start or at the end of the 3 months trial period. However, there were two groups of patterns that seemed to show a distinct effect of the start and end of trial appointments. One group upheld 'good' adherence for a period after the clinical appointment and then their adherence rate deteriorated. The other group showed 'good' adherence rate both at the start and the end of the trial period, with a distinct decline in adherence rate in the middle. The final distinct pattern that emerged was the Dosette box users. In this group were two patients who normally would use Dosette boxes and had influenced the MEMS data so that it seemed they had missed more doses than they reported to have missed in the interviews.

What was particularly interesting was that where patients' narratives and MEMS recordings were not congruent it was at times possible to discern what had really happened, although MEMS simply showed missed doses. This shows the limitation of measurements such as MEMS in capturing the full complexity of patients' medication taking behaviour. In addition, it highlighted the impact that trial methods can have on patients' adherence rates, and it might question the ethics of using MEMS during long-term trials if it hinders patients from using adherence aids that may benefit them. This data is unique, as to the best of my knowledge there are no studies that have qualitatively linked patient narratives and MEMS data in this manner (where the patients were largely unaware of being monitored).

Nonetheless, in order to implement the deeper understanding of patients' medication taking behaviour to work towards solutions that may improve patients' adherence, the MRC in the UK recommends that the intervention development phase is theory driven (Campbell et al., Craig et al.). Chapter 3 therefore investigated the usefulness of the ACF to explain the patients' reasons for missing doses of imatinib.

5.2.2 THE USEFULNESS OF THE ACCIDENT CAUSATION FRAMEWORK TO EXPLAIN PATIENTS' REASONS FOR NONADHERENCE

The Accident Causation Framework (ACF; Reason, 1990; 2001) was found to be useful when explaining CML patients' nonadherence to imatinib, and may be

applicable to explaining nonadherent behaviours in general. Nonetheless, adaptations were suggested to enhance the frameworks ability to explain nonadherence and to make the terminology better suited to the field of treatment adherence. The arguments in support of the adaptations were discussed in detail in chapter 3 (section 3.5.1.3, pp. 216) and will not be repeated here. Consequently, the framework could explain the causes of intentional and unintentional nonadherence that was represented in the sample and provided a wider system perspective of the different defence strategies that seemed to have reduced the incidence of nonadherence. The adapted framework can be seen in Figure 24 (pp. 221).

According to the ACF analysis slips and lapses leading to forgetting to take doses of imatinib were the most common causes of unintentional nonadherence. In addition, the framework can explain nonadherence caused by constraints (physiological barriers) to adhere to treatment and for nonadherence caused by direct influences of system or organisational causes such as restricted access to imatinib and prescribing or communication errors.

In terms of intentional nonadherence the most common reason was rationalised nonadherence, where the patients knew the correct process to take the imatinib, but had for some reason decided to not take it as prescribed. Knowledge based nonadherence (caused by the patient having to work out how to act in a situation not encountered before) and rule based nonadherence (when patients use a mistaken rule of action for specific recurrent situations in the belief it was the correct thing to do) were very rare in this sample. However, these types of nonadherence may be more common during the early stages of starting with a new treatment.

Defences were represented by a range of strategies that patients had used to support their adherence, including the use of adherence aids as well as instances where nonadherence had been detected and addressed by health care providers. An adaptation worth highlighting is the representation of the feedback loop transferring information of the detection of nonadherence, or adverse consequences from nonadherence, to warn higher levels of the system (including

health care providers and patients). Consequently, interventions could be put in place to address the problems. Moreover, interventions to protect patients from the causes of nonadherence and recovery from consequences of nonadherence are likely to include monitoring of adherence rates or other indicators of adherence such as clinical response, which would thus be represented by the feedback loop.

5.2.3 DEVELPMENT AND PILOTING OF THE DIAGNOSTIC ADHERENCE SCALES

Valid and easily administered adherence scales are needed to support both research and practice. For this purpose, chapter 4 presented the development and piloting of two versions of a novel retrospective adherence scale, the DAS-specific for a single medication and the DAS-multi for multiple medications. These scales were developed in accordance with the ACF and firmly grounded in the relevant literature.

Pilot studies were conducted in order to reveal potential flaws in design and study methodology so that these can be addressed and improved before a larger scale evaluation. Typically, during the process of developing a new scale, the measurement items go through several stages of piloting and revising until the pilot studies can detect no more problems with the measurement and it can be considered ready to be tested in a larger scale validation study.

The results from Pilot A indicated that there was not a significant difference between patients' adherence rate during the 7 days preceding a hospital appointment and longer term adherence rates, within the period that was monitored with MEMS. This suggests that the 7 days recall period may be representative of longer term adherence rates and supports the use of this limited recall period to measure patients' adherence rates by self-report.

Pilot B supported face and content validity of the DAS-specific, as well as ease of use and acceptability. Content validity was further supported by the strict theoretical basis of developing the DAS-specific items.

Pilot C tested concurrent validity of the DAS-specific against MEMS in 17 patients, as well as sensitivity, specificity and predictive values. There were many discrepancies between the DAS-specific and MEMS. In most cases the DAS-specific led to an underestimation of adherence rates, but in one case the DAS-specific overestimated the adherence rate compared to the MEMS. It may suggest that the DAS-specific is not a valid measure of 'true' adherence rates. However, it also raises questions regarding the best way to test concurrent criterion validity; in particular considering MEMS is often thought to be the 'gold standard' but is not without its flaws and limitations.

Subsequently, we developed the DAS-multi, which is an interviewer-administered version of the scale for testing adherence rates to multiple medicines. The DAS-multi is meant to test adherence rates and capture intentional and unintentional nonadherence by the same method as the DAS-specific. However, information regarding multiple medicines and adherence rates are all recorded on a single recording sheet. The DAS-multi has not yet been piloted.

Consequently, the DAS-specific and the DAS-multi have shown some promise to become easily administered adherence measurement scales that can be used to measure change in adherence rates over time, although further validation studies are needed before the measures can be recommended for use (or not). Furthermore, the scales ability to dichotomise intentional and unintentional nonadherence has not yet been validated. Finally, we have not yet validated an interviewer-administered version of the DAS-specific for single medicines, or a patient completed version of the DAS-multi for multiple medicines.

5.3 IMPLICATIONS FOR POLICY

This thesis suggests that we can further our understanding of behaviour, theory and measurements by taking a wider system perspective. In terms of behaviour, the system perspective explains how factors within the individual as well as within the wider health care system, including HCPs, health organisation and health policy, can influence behaviour. In terms of theory, the perspective can explain the interaction of these factors and can provide the theoretical basis of interventions

to improve the system and reduce the incidence of nonadherence. In terms of measurement, the system perspective highlights the need for measures suitable for continuous monitoring of adherence, measure that can also be used to inform routine feedback within the system of rates of nonadherence. Therefore, it is suggested that the novel contributions to knowledge and critical thinking presented herein has a wider applicability to the adherence research field, clinical practice and health policy in general.

There has previously been very little research exploring cancer patients' medication taking behaviour and their reasons for missing doses. Consequently, there is limited understanding of the issues facing these patients and how we can improve the system to reduce the incidence of nonadherence to oral cancer therapy. This is of concern as oral anticancer drugs are increasing in availability and use (Aisner, 2007, NPSA, 2008, BOPA, 2004).

In order to seek excellence in treatment and outcomes of cancer care, policy documents setting out future directions should link in with policy drivers of improving patients' adherence (Nunes et al., 2009), as well as the general policies on continuous quality improvement of health care services, safety and outcomes (DoH, 2010, DoH, 2008). Currently the cancer reform strategy does not mention the issue of potential nonadherence to treatment amongst cancer patients (DoH, 2007). However, the evidence base showing widespread nonadherence and associated negative consequences amongst cancer patients is growing and the issue of nonadherence to medication is becoming an increasing priority in the UK (Nunes et al., 2009). As a result, organisations and governmental bodies, such as the Department of Health, may take action and link adherence and cancer care policies in future documents and guidelines. A consequence of setting out clear guidelines to address nonadherence in cancer populations is likely to an effect on system level factors related to adherence, such as influence the availability of funding opportunities for research and prompt individual health care organisations to provide adherence enhancing services. Furthermore, the system view of working towards solutions to reduce instances of nonadherence, as explained by the ACF, calls for further research and critical evaluation of current

health policies and their impact on individual patients' medication taking behaviours.

5.4 IMPLICATIONS FOR RESEARCH

The thesis presents for the first time an exploration of CML patients' experiences with using an oral anticancer drug. This means that the knowledge presented herein can lay the ground work for future research. Evidently, the knowledge will apply specifically in the area of treatment adherence in CML patients, but may also contribute towards the understanding of cancer patients' adherence to oral anticancer drugs more generally. This exploratory work can be used to inform future quantitative studies, for example in search of the factors that best explain and predict nonadherence in these patient populations. Future research also requires accurate measures of adherence rates and Chapter 4 presented the development and piloting of a new adherence measurement scale that may be used for this purpose.

Furthermore, the thesis may inform research on the development and evaluation of interventions aimed at reducing nonadherence in CML patients prescribed imatinib. The interview results suggest that interventions should primarily focus on improving the management of side effects and support patients in remembering to take their doses correctly.

Nonetheless, interventions have to be developed and evaluated appropriately before they are implemented in practice and such research should be firmly based in theory (Campbell et al., 2000; Craig et al., 2008). The ACF has the advantage over the social cognition theories (SCT) that it can explain unintentional nonadherence as well as intentional nonadherence. This is beneficial when developing interventions as these two types of nonadherence have different causes that need to be addressed (WHO, 2003, Nunes et al., 2009, Horne et al., 2005). In addition, the ACF can also incorporate other specific approaches to explain nonadherence. For example, we know that beliefs about medicines influence intentional nonadherence and the patients' motivation to adhere to treatment (Clifford et al., 2008). Reason argues in his 2001 book chapter on medical errors that "violations

[the most common intentional nonadherence in the interview sample] require motivational and organisational remedies" (pp. 13-14). This suggests that we need to focus on both motivation issues (i.e. beliefs) as well as organisational influences (such as HCP's feedback) to develop defences/interventions that aim to reduce intentional nonadherence.

In addition, several patients mentioned having worked out themselves what sort of food is better to take the imatinib with, including toast, pasta and Kitkat chocolate bars. Consequently, if certain food groups can help relieve side effects then that may improve quality of life, which may in turn lead to improved adherence. This suggests that a possible area for future research is to investigate the effect of diet on side-effects.

5.5 IMPLICATIONS FOR PRACTICE

The thesis may also inform practice. Patients need to be provided support to deal with side-effects and need to have access to adherence aids, such as monitored dosing boxes and alarms, which are available. In cases where reduction of side-effects is not possible, solutions may include psychological interventions aimed at empowering patient to cope better with side-effects. Finally, in cases where side-effects are too severe it may be necessary to discontinue imatinib treatment and consider alternative treatments (Viele, 2007), which should ideally be a shared decision taken by the prescriber and the patient in concordance {DoH, 2010).

In addition, it was evident from the interviews that the patients relied on their clinicians to let them know if their nonadherence had adverse effect on their outcomes. In addition, nonadherence may be the predominant reason why some patients fail to obtain adequate clinical response on imatinib (Marin et al., 2010). Therefore, HCPs should be vigilant for signs of nonadherence and consider this as an option when a patient is not responding well to imatinib therapy. Indeed, nonadherence may be worth considering in all instances where patients are not responding well to self-administered therapy as nonadherence has been associated with reduced clinical response in a range of illness groups such as HIV

and asthma (Simoni et al., 2006; Horne et al., 2006; Ciechanowski et al., 2001, Lucas et al., 2005).

It is also important to make sure that the systems are in place to provide treatment without hindrance. For example, there was one interviewee who went for nearly one week without imatinib because the pharmacy had run out of stock and another patient who had been prescribed too few doses to last him until the next appointment. These are two areas where system improvements may be able to reduce external causes of unintentional nonadherence.

5.5.1 ROUTINE MONITORING OF ADHERENCE

Routine monitoring of adherence rates would be a key component to monitor the ongoing effectiveness of adherence services and interventions. However, routine monitoring may feel intrusive to patients and could thus have an adverse rather than a positive effect on the patients' general well being and adherence rates. Careful consideration therefore has to be taken before implementing such monitoring in clinical practice; in particular, with regards to how such information should be used and to what extent patients should be involved in the process. In addition, the patients should always be allowed the choice of not adhering to treatment {Haynes, 2002}; therefore, maybe the choice of not being monitored should also be respected? In that case it would be difficult to know whether patients who chose not to be monitored are more or less likely to adhere to treatment as prescribed.

It may be possible to involve patients in the process of routine monitoring and use this as a vehicle to engage in communication about adherence issues. One way to do this could be to use MEMS monitoring with the patients' knowledge. The adherence data collected could be shown to the patient in the form of the diary view and/or the chronology chart and discussed in clinic. This may open up a discussion about why individual doses were missed and the causes could be addressed. A study into the effect of adherence to an anti-fungal prophylaxis on infections in women with HIV, found that the women were:

> ...very enthusiastic seeing the computer display ...//... often wanted to know their compliance rates ...//... and were encouraged when they saw they had been compliant. In addition, during refill appointments with the MEMS readings, the patient would often explain why the medication dosages were missed on certain days... (Geletko et al., 1996, pp 1341).

Indeed, MEMS feedback has previously been used as an adherence enhancing intervention. For example, Schmitz et al. (2005) studied whether pill-taking instructions and personalised feedback using MEMS data would enhance adherence to bupropion-SR for smoking cessation in women during a randomised controlled trial. The results showed that the intervention group maintained a higher adherence rate over time compared to the control group ($p=0.0003$) (Schmitz et al., 2005). These results suggest that monitoring and personalised feedback to address causes of nonadherence may be beneficial to improve patients' adherence rates. The MEMS devices they used in the Schmitz et al study were the same as the ones used in our clinical trial (Marin et al. 2010), which was described in chapter 2 of this thesis.

Rosen et al (2004) conducted a similar adherence intervention study with diabetes patients who had been prescribed metformin. This study used a MEMS device that displayed the number of openings recorded each day and the hours that have passed since the cap was last opened. In addition to providing personalised feedback of the MEMS results to the patients, the intervention consisted of dose-cue training. Dose cue training involved the patients being asked to consider cues that may remind them to take their medication. The adherence rate increased significantly more in the intervention group over time compared to the control group ($p=0.017$). However, visual inspection of the follow up data in the paper showed that adherence rates declined in the intervention group after the intervention had been discontinued (Rosen et al., 2004).

This indicates that although MEMS feedback can be helpful in improving adherence rates during a time period, it is unknown whether the intervention has a lasting effect. It could be that ongoing feedback and support is needed to maintain a

higher adherence rate, or indeed it could be that patients' adherence rates tend to decline as they get used to the new routine and fall back into old habits. In addition, it is important to consider the impact that the MEMS can have on established routines that the patients use to manage their medication regimen. For example, if the patient uses a Dosette box s/he may find it more difficult to remember to take their medication if they are coaxed into using a MEMS device instead.

5.5.2 ADDRESS PATIENTS' MISCONCEPTIONS OF THE CONSEQUENCE OF MISSING DOSES

Moreover, several patients who stopped taking imatinib during certain periods tended to rely on the imatinib to work as soon as they started to take it again; in their experience this had always worked before. This might be because the PCR allows for close monitoring of clinical response in CML patients, thus the patients may trust that potential adverse consequences will be detected early enough for them to reinitiate their adherence to imatinib. This could be seen as a reasonable argument and suggests it is alright for patients to take 'drug holidays'. However, some patients can develop resistance to imatinib and lose their response (Apperley, 2007a, 2007b). Furthermore, we showed that nonadherence was the strongest predictor of response in the clinical trial patient population (Marin et al., 2010). The one year follow up data of the trial shows that the patients who were nonadherent during the clinical trial were significantly more likely than adherent patients to lose their complete cytogenetic response ($p= 0.0002$) and less likely to remain on imatinib therapy ($p=0.006$) (Ibrahim et al., In press). These results further suggest that the belief that imatinib will always work if treatment is stopped and reinitiated in periods may be misguided and patients need to be made aware of this.

Nonetheless, the research suggesting a causative link between imatinib adherence and clinical response in CML is very recently published (Noens et al., 2009; Marin et al., 2010; Ibrahim et al., In press); none of this was known at the time when the interviews were conducted. It is therefore possible there is already a change in acknowledging the occurrence of nonadherence and the associated consequences,

thus health care providers may already be approaching the issue of nonadherence somewhat differently in clinical practice today.

The interview results seems to suggest that if patients were more aware of the consequences of nonadherence and better informed of their clinical response they would be more adherent. However, we cannot make assumptions regarding how potential feedback of clinical response will influence the patients' perception of treatment or behaviour. For example, research from patients with HIV has shown that patients' subjective experience of their illness is more important when evaluating their treatment than objective measures of treatment efficacy (Pound et al., 2005). Indeed, in the interview sample, positive feedback of response seemed to have increased nonadherence in some patients, but it would be unethical and most likely detrimental to most aspects of care and well being for the patients to only focus on giving negative clinical feedback.

In line with the system approach, the interviews revealed that factors within the patients' environment in the health care system may have influenced their nonadherence. For example, HCPs seemed to reinforce nonadherence through feedback given to patients regarding their clinical response and regarding the risk associated with planned treatment interruptions. This type of communication seemed to have made many patients believe that it did not matter if they missed "the odd dose" (which could be as many as 2 doses or more per week). Indeed, communication is thought to be the most important factor that mediates HCPs influence on adherence rates (Alexander et al., 2006). In addition, one patient said he did not think it mattered if he missed doses at times based on information provided in the imatinib information leaflets. This is consistent with findings that information leaflets do not increase patients' knowledge about of their illness and treatment; although there is little evidence information leaflets influences adherence rates (Raynor et al., 2007). Consequently, the results suggest that solutions to reduce the incidents of nonadherence should not just target individual patients, but should also target the information flow within the health care system. This may include education and training for health care providers, as well as clearly set up practice guidelines.

5.6 THEORETICAL REFLECTIONS

The Accident Causation Framework can explain both intentional and unintentional aspects of behaviour; however, it cannot explain positive behaviour (i.e. adherence). The social cognition theories, on the other hand, can explain both why patients choose to adhere and why patient choose not to adhere. Reason's later texts (e.g. 2008) do highlight the importance of examining positive aspects of behaviour, so called "heroic recoveries". In essence, knowledge gained by examining positive aspects of behaviour, i.e. adherence behaviour, within the domain of the ACF can be used to inform the development of better defences/interventions to reduce the incidents of nonadherence. However, the framework cannot explain these positive aspects of behaviour.

The question is how important it is to account for positive aspects of behaviour when what we want to achieve is an absence of negative behaviour, i.e. absence of nonadherence (absence of errors and violations). Maybe it is more helpful when developing interventions if we can account for all aspects of nonadherence and less important to explain achieved adherence? Nonetheless, there seem to be a general movement towards researching positive aspects of behaviour and specific calls have been made for research into adherence, instead of just focusing on nonadherence (e.g. Pound et al., 2005). As mentioned above, the advantage of researching "heroic recoveries" in error research has been highlighted in the literature (Reason, 2008) and new disciplines, such as 'positive psychology' are evolving (Snyder and Lopez, 2002). It is likely to come a day when research will call for a theory that can account for adherence, as well as intentional and unintentional nonadherence.

Furthermore, there has been some debate in the literature about whether it is the right way forward to understand nonadherence by focusing on the whole system, and thus reduce personal blame on patients for their nonadherence (Buetow and

Elwyn, 2006, 2007). Buetow and Elwyn (2006; 2007) define nonadherence as an error in line with the ACF and argue that patients are morally responsible for their nonadherence because nonadherence is ultimately expressed through patient behaviour. The authors further argue that patients should thus be held responsible for the success or failure in avoiding nonadherence.

Buetow and Elwyn (2006; 2007) adopt a rather judgemental stance in relation to patients' nonadherence and seem to overlook the causes and reasons behind such behaviour. It may be less important to argue over what direction to point the finger than to focus on all factors that influence nonadherent behaviour – be it personal, environment or organisational – and work towards finding solutions. It is possible that having adapted terminology and theory appropriately to explain nonadherence will reduce some of the emotive tension that is inherent in using value-laden language of error, blame and moral responsibility.

The reduction of personal blame is pivotal in the system approach to understanding errors. Indeed, blame is considered the most harmful and counterproductive in reducing errors within a system as it fosters denial and inhibits reporting of errors and 'near misses' that can inform system improvements (Reason, 2008). However, a blame free approach can be difficult to implement in health care practice when considering errors and mistakes committed by health care providers; in particular errors committed by pharmacists who are bound by criminal law in relation to dispensing medication and can be charged independent of whether their error caused harm to patients or not (Nathan, 2004).

Therefore, more recently the idea of "fair blame" has been introduced in relation to health care (Timbs, 2007). The "fair blame" culture encourages people to report errors to allow learning from mistakes to inform improvement strategies. However, when things do go wrong, it is argued, the people involved has to take responsibility for their actions (Timbs, 2007). Nonetheless, in relation to the patients' medication taking behaviours the blame free approach may be beneficial and encourage an open dialogue between health care providers and patients about adherence issues when working towards solutions to reduce nonadherence, as the

current UK health policy context promotes (DoH, 2010). In terms of the patients' actions perhaps less consideration has to be taken from a legal perspective; patients ultimately have the right to not adhere (Haynes et al., 2002). The challenge may rather be to integrate the blame free culture in relation to patients' nonadherence with the "fair blame" culture of medication errors, if these two concepts are to be considered within the same framework of medical errors.

5.7 LIMITATIONS

There are some general limitations of this thesis, in addition to the limitations that are specific to the individual studies and were discussed in chapter 2, 3 and 4 respectively.

The aim of this thesis was to better understand nonadherence in cancer patients who had been prescribed oral anticancer drugs. To this aim the research used chronic myeloid leukaemia (CML) patients prescribed imatinib as the paradigm of investigation. However, CML is a rare form of cancer in the UK with about 650 patients diagnosed each year (NICE, 2010) compared to the 298,000 new cases of cancer diagnosed in the UK each year (CRUK, 2010). In addition, in terms of oral anticancer treatments dispensed yearly in the UK, imatinib account for 6% of the total number of dose units, which includes imatinib prescribed for both CML and gastrointestinal stromal tumours (data for the year 2006-2007 NPSA, 2008). This means that CML patients on imatinib could be considered a limited population for making generalisations about cancer patients' adherence to oral anticancer drugs.

In addition, imatinib is a highly efficient drug. For the CML patients who are responding well to imatinib, by achieving complete cytogenetic response (CCyR) or major molecular response (MMR) at 18 months, the 5 year progression-free survival is 97%-99% (Apperley, 2007a). Indeed, for the patients who reach MMR the risk of illness progression is reduced each year of continued treatment and after the third year the risk is zero (Apperley, 2007a). All of the patients included in the interviews had been on imatinib for at least two years and all had achieved at least a CCyR. This means that the issues affecting the patients in this sample, as well as CML patients in general, may be different from the issues other cancer

patients are faced with, where the treatments are less effective and illness progression more likely. In addition, many other cancers, such as breast cancer, are often treated with a combination of different drugs (Ruddy et al., 2009), which in turn may affect adherence.

The thesis also aimed to explore the usefulness of using the Accident Causation Framework to explain nonadherence from a system perspective. A limitation of the methods used in this study was that the reasons for nonadherence, which were explored from system perspective, were captured and analysed solely based on the patients' narratives. This aim may have been better fulfilled had the analysis included data from other sources within the system to allow for a clearer picture of the whole system and the interactions that may have affected individual patients' adherence rates.

The aim to develop and pilot a novel adherence scale was fulfilled, although there were limitations with this research. In particular, Pilot B was done in convenience samples with very few participants who were nonadherent. We would have been better able to pilot the psychometric properties of the DASs ability to measure differences in adherence rates had more patients been nonadherent.

5.8 FUTURE RESEARCH

The novel contributions of this thesis to knowledge and critical thinking in the field of medication adherence can inform future research both in the specific fields of adherence to imatinib and other oral anticancer drugs, as well as in the wider medication adherence field.

In terms of CML patients' adherence to imatinib, the next step is to design quantitative studies to test the generalisability of the reasons for not taking imatinib as prescribed that were identified. In addition, there are several second line tyrosine kinase inhibitors that are currently being evaluated by NICE for use in CML, such as nilotinib and dasatinib (NICE, 2010). Patient adherence and potential adverse consequences should be further investigated in these drugs as well. In particular, since nilotinib, in contrast to imatinib and dasatinib, has to be

administered twice daily with 12 hours interval and requires patients to fast 2 hour before taking each dose and for 1 hour after (Novartis Oncology, 2010); this is bound to make it considerable more difficult for patients to adhere to treatment, which may in turn have adverse effects on health.

The results suggested that many nonadherent patients had been reinforced in their belief that missing 'the odd dose' does not matter through communication with health care providers, including clinicians and pharmacists. This belief was expressed by both intentional and unintentional nonadherers. However, it was also mentioned by patients who adhered nearly perfectly. It has previously been suggested that appropriate patient-provider communication may be particularly important in cancer care, but that little is known about the ways communication affect cancer patients' adherence (DiMatteo, 2003). This calls for further research into the role of communication in influencing patients' adherence in CML patients in particular, as well as in cancer patient populations in general.

Research should also quantitatively test the components of the ACF and association with nonadherence. Further development of the framework should include mapping out the whole system that may influence nonadherence to medication. This could include interviewing different stakeholders within the system, such as pharmacists, clinicians, reception staff that book appointments, managers and policy developers; and a clearer picture of the complete system and interactions may then emerge.

Furthermore, if the ACF is found to explain general causes of nonadherence it can be used to theoretically drive the development of adherence enhancing interventions. The ACF has the potential of being superior to other theories in designing adherence enhancing interventions as it allows for both intentional and unintentional causes to be addressed, as well as wider system factors that are beyond the patients' control. As already mentioned, intervention development should ideally be theory driven and randomly controlled to identify the active components and evaluate the effectiveness (Craig et al., 2008, Campbell et al., 2000).

In addition, to support further adherence research using the ACF measurements should be developed accordingly. Thus far the DAS-specific and the DAS-multi has been developed according to the same theoretical basis. However, the psychometric qualities of these measures have not yet been completely established and cannot be recommended for use if further research and practice until this is done. The details of future validation studies of the two versions of the DAS was discussed in detail in chapter 4 sections 4.4.2 (pp. 269) and 4.4.3 (pp. 271), and will not be repeated here.

Finally during the patient feedback session several patients suggested research into the effect on diet on side effects as several have themselves figured out which foods reduce their own side effects. There is to the best of my knowledge no current research into "safe-foods" and the effect of diet on side-effects in CML patients taking oral anticancer drugs. However, there is not a significant clinical effect of food on oral bioavailability of imatinib (Smorenburg and Sparreboom, 2006), thus if certain food groups can help relieve side effects then that may improve quality of life for many patients suffering from nausea and other side effects. This may in turn lead to improvement in adherence.

5.9 CONCLUSIONS

This thesis has presented specific knowledge regarding chronic myeloid leukaemia patients' reasons for nonadherence for the first time. This knowledge forms a basis on which to build future research and adherence interventions to support patients with CML to adhere optimally to their oral anticancer treatments. Moreover, the knowledge may be applicable in relation to other cancers that can be treated with self-administered oral drugs and inform policy developers.

Taking a system perspective furthered our understanding of patients' reasons for nonadherence and the Accident Causation Framework has been adapted to better explain medication nonadherence. The Accident Causation Framework allow for the whole system to be analysed, including different defence mechanisms to detect and reduce incidents of nonadherence and feedback to disseminate such information within the system. The thesis has also presented four pilot studies

testing the validity a novel self-report adherence scale. Hence, should further validation support the use of this scale it could be recommended for use in research and clinical practice to monitor adherence rates.

The advances in understanding adherence behaviour, theory and measurement, contributed by this thesis, can be used to drive future research taking a system perspective when working towards solutions to support patients' use of medicines.

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Imperial College Healthcare NHS
NHS Trust

PATIENT INFORMATION LEAFLET

Adherence to Imatinib in Adult Patients with Chronic Myeloid Leukemia

6th November 2008

Name of study protocol: LE_imatinib_v1(041008).rtf

Please read this document carefully

You are being invited to take part in a research interview. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask the researcher (contact details on last page), your clinician or nurse if there is anythingthat is not clear or if you would like more information.

Take time to decide whether or not you want to take part.

Thank you for reading this.

You will be given a copy of this information sheet to keep

Reason for the study, why I have been invited and what taking part will entail for me

1. What is the purpose of the study?

Imatinib (a tyrosine kinase inhibitor) has revolutionised the treatment of chronic myeloid leukaemia (CML). The first clinical trials with Imatinib/Gleevec® were conducted in 1998 in patients with advanced disease. By 2002 Imatinib was established as the standard therapy for all patients including those recently diagnosed.

In spite of overwhelming evidence about its efficacy, individual treatment response varies. The variability may be related to the way people take their Imatinib. It is common that patients sometimes forget doses, change the dose and take more or less than prescribed. However, we do not know enough about what factors influence the way people take their medicines and why some people experience difficulties. Therefore, the purpose of this study is to interview patients to learn more about their experience with taking Imatinib. The knowledge we gain from the interviews will teach us how to best support patients to take their Imatinib optimally.

2. Why have I been chosen?

You are being asked to consider participating in this study because you have chronic myeloid leukemia and you have been taking Imatinib for a long period of time. We are inviting patients who were prescribed Imatinib as the initial treatment when first diagnosed with chronic myeloid leukaemia. All the patients we are inviting have also participated in the trial that you recently completed, which looked at Imatinib use, side effects and treatment response.

3. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and we will ask you to sign a consent form. You are still free to withdraw at any time and without giving a reason. If you decide against taking part in this study or you join the study now but later decide that you want to change your mind you are completely free to do so. You do not have to give a reason for your decision. Whatever you decide it will not affect your relationship with the usual doctors and nurses looking after you or your further medical care.

4. What will happen to me if I take part?

You will be invited for an interview to share your experiences with taking Imatinib. The interview will take about 45 minutes, but depends on how much you want to talk about. You will only have to meet with the researcher on this one occasion.

The interview will take place either at your hospital or at your home, which ever you prefer. At the interview you will be introduced to the researcher, Miss Lina Eliasson, who will listen to and record what you say. Miss Eliasson will ask if she may tape-record the interview so that it is easier for her to listen to what you have to say. However, if you do not want to be recorded you may say so and Miss Eliasson will take handwritten notes instead.

5. **Are there any payments?**

There will not be any payments for your participation in this study.

6. **What are the possible disadvantages and risks of taking part?**

We do not anticipate any disadvantage caused by taking part in this study aside from your personal effort and time.

7. **What are the possible benefits of taking part?**

We not expect any benefit to you personally for your participationin this study. We hope that the results of this study may help doctors to learn more about the use of Imatinib in the management of chronic myeloid leukemia.

8. **What will happen if I don't want to carry on with the study?**

Your participation in this study is voluntary. You don't have to be in this research study at all. You can agree to be in the study now and change your mind later. Your decision will not affect your regular care or the benefits to which you are otherwise entitled.

9. **How do I withdraw my consent to participate in this study?**

To withdraw your written consent you simply tell a member of the research team you would like to do so. You do not have to state a reason for withdrawing your consent, and you will not be asked to explain why.

You can withdraw your consent at any time. Before the interview is started, during the interview or directly after the interview has been completed (up to 24 hours after the end of the interview). If you withdraw your consent during or directly after the interview, all information that has been recorded will be deleted and will thus not be used by the researcher.

Problems, confidentiality and how the research will be reported

1. **What if there is a problem?**

The School of Pharmacy, University of London, holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that the School of Pharmacy is at fault. This does not affect your legal rights to seek compensation. National Health Service complaints mechanisms are also available to you. All details can be obtained from the hospital.

2. **Will my taking part in this study be kept confidential?**

All personal information about you collected for this study will be kept confidential and you will not be identified by name. Instead a study number will be used in all documentation relating to the study.

The information you tell Miss Eliasson in the interviews is completely confidential and will not be passed on to your doctors, nurses or any other hospital staff, whatever you have to tell.

3. **What will happen to the results of the research study?**

We will keep your information confidential. This means that the only person who will have access to your information and the only person who will listen to what you said in your interview is the interviewer.

After the interview what you said will be written out word by word. This document will be made anonymous. Anonymous means that there will be no way to identify you from the information given in the documents. If you have made references that can indirectly be used to identify you, such as a recent holiday or unusual hobby, care will be taken to change these. After the written documents have been made anonymous the interviewer's two supervisors will have access to the information.

However, your doctor or any one else working at the hospital will NOT be allowed to listen to your interview and will NOT have access to any of the information you have given us. If you would like to have a copy of the questions asked and your answers, we will send you a copy.

The results will be reported as part of the doctoral thesis, which might include quotes taken from your interview, and may also be published in medical journals. However, we will ensure there is no way for anyone to identify you or find out which quotes are yours in any documents related to the study.

4. **Who is organizing and funding the research?**

This research is part of a doctoral thesis and is funded by the School of Pharmacy, University of London.

5. **Who has reviewed the study?**

This study was given a favorable ethical opinion for conduct in the NHS by Lewisham Research Ethics Committee.

6. **Contact Details:**

If you have any questions that remain unanswered about the study, please ask the study researcher, Miss Lina Eliasson.

Name: Miss Lina Eliasson
Email:
Telephone:

You can obtain further advice about participating from the research nurses, your clinician, support nurses or your local GP:

Research Nurses (during office hours):

Out of office hours call Hammersmith Hospital on 020 8383 1000 and ask for the Haematology Registrar on call.

The department also has 3 support nurses to whom the patients have access to and can be referred to by the research nurses or investigator.

If you want further information regarding taking part in research:

Any member of the public has access to the COREC website which contains up to date information on all aspects of conducting & taking part in clinical trials under an area called "Patients & Public": http://www.nres.npsa.nhs.uk/patients-and-the-public.

The Involve website provides information about public involvement in research: http://www.invo.org.uk (formerly consumers in NHS Research).

The Department of Health's consent home page gives guidance about giving informed consent: www.dh.gov.uk/policyandguidance/healthandsocialcaretopics/consent/fs/en.

Further information related to trials can be found at National Electronic Library for Health http://www.library.nhs.uk/trials

If you want to make a complaint regarding this study you can contact:

Any questions should be directed to the study researcher or you can contact PALS (Patient Advice Liaison Service) at Hammersmith Hospital on 020 8383 1000.

In addition, the School of Pharmacy is holding indemnity policies that cover the design and conduct of this study; contact details are displayed below:

The School of Pharmacy
University of London
29-39 Brunswick Square
London
WC1N 1AX
United Kingdom

Switchboard: 020 7753 5800

Imperial College Healthcare NHS
NHS Trust

PATIENT CONSENT FORM

Adherence to Imatinib in Adult Patients with Chronic Myeloid Leukemia

1. I confirm that I have read and understand the patient information sheet dated 6th November 2008 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that information from my medical records, regarding the treatment I am receiving, will be given to the researchers where it is relevant to my taking part in this research. I give permission for these individuals to have access to information regarding my treatment. ☐
4. I understand that my medical data will be collected for this study and may be used to help develop new research, and that data protection regulations will be observed, and strict confidentiality maintained. ☐
5. I agree to take part in the above study. ☐

Name of Patient (please print)	Date	Signature
Name of person obtaining consent	Date	Signature

1 for patient, 1 for hospital notes, 1 for researcher site file

Topic Guide for Interviews

Adherence to imatinib in adult patients with chronic myeloid leukaemia

This is a list of topics that will be raised during the interview. The conversation will mainly be guided by what the patient has to say, in accordance with the study methods.

- Brief introduction of study and introduction of interviewer
- Written consent taken and reminder that patient may terminate interview at any time
- Description of a typical day in the patient's life; hobbies, work, living and family
- Patient's daily routine in relation to using imatinib and other medicines
- Methods that the patient uses to facilitate medication taking
- The patient's account of the last time they missed/changed a dose?
- Other examples of missed/changed doses
- Co-therapies currently taken by the patient
- Missed/changed doses of co-therapies
- Social support – family, friends
- Relationship with doctors

Topic Guide for Interviews

Adherence to imatinib in adult patients with chronic myeloid leukaemia

Introduction

- Written consent – data is confidential and will be made anonymous
- Study and Interviewer
- Reminder that patient may terminate interview at any time

Start-up questions

- Description of a typical day in the patient's life; hobbies, work, lifestyle, family

CML

- Your illness – time of diagnosis
- Any other conditions

Imatinib

- **What is your experience of Imatinib? What do you think about it?**
- Regimen – dose / time – length of treatment
- Patient's daily practice using imatinib
- **Very common that patients at time miss a few doses, thinking of the past 7 days have you:**
    - Missed any doses?
    - Taken any doses late?
    - Changed the dose, and taken more or less than the doctors say?
- **Ever missed a dose?**
- Methods to facilitate medication taking
- Side-effects
- Thoughts on effectiveness of imatinib
- Co-therapies

Social

- Work / Education / Religion
- Family / Friends

Health care

- Access to services
- Relationship with doctors / Nurses
- Alternative medicines / Natural products (re beliefs in medicines)

Information

- Information about treatment and illness

Close

- What is you feeling about Imatinib?
- Anything else you would like to tell me?

APPENDIX D: PATIENT INFORMATION RECORDING SHEET FOR NURSES

Patient number: _____

Sex: Female / Male

Time of diagnosis:_____

Approximate appointment cycle, Hammersmith AND local (if known) – e.g. every 3 weeks, every 2 months:

_____

Regime for CML:_____

Co-morbidities:_____

_____

Co-therapies:_____

_____

Response to treatment:_____

_____

Adherence data MEMS:_____

_____

Adherence data – PILL COUNT:_____

_____

Adherence classification: Adherent / Nonadherent

Notes: _____

APPENDIX E: PATIENT FEEDBACK FORM – TRIAL AND INTERVIEWS FEEDBACK SESSION

Imatinib trial results feedback session
Feedback form

Please tick the box to describe who you are:

☐ I participated in the trial ☐ I am related to a person who participated in the trial

☐ I am a health care professional ☐ Other, please state_____

		Please tick one response				
		Strongly Agree	Agree	Not Sure	Disagree	Strongly Disagree
1	I found Part 1 'What dose is taken – measuring behaviour' informative					
2	It seems MEMS, the electronic caps for the trial's medicine bottles, are useful for these types of trials					
3	I feel uneasy about the use of MEMS					
4	I think they should use MEMS for similar trials in the future					
5	I think they should have told us/the patients they used MEMS before starting the trial					
6	I found Part 2 'Feedback of the trial results' informative					
8	I found Part 3 'Presentation of interview results' informative					
9	I feel the interview results gave a good picture of issues related to how I take my imatinib/Gleevec ☐Please tick if you are NOT a patient					

10. Please record below any other feedback/comments about this feedback session: