Understanding and quantifying adherence
and its link to therapeutic success

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ABSTRACT

It is known that increased adherence to appropriately prescribed drugs is associated with better therapeutic outcomes and contributes to lower mortality. Adherence is described by three processes, namely initiation, implementation and discontinuation. The use of electronic monitoring e.g. Medication Event Monitoring System (MEMS) has enabled a quantitative understanding of the three processes of adherence. This includes delayed initiation, early discontinuation and particularly those around implementation including timing variability, random missed doses and drug holidays. There have been many attempts to improve adherence. An alternative approach to assist patients with suboptimal adherence to still attain therapeutic success lies in the choice of forgiving drugs. Forgiveness is a drug specific property that determines how sensitive therapeutic success is under imperfect adherence.

The overarching aim of this thesis was to quantify adherence, influences of factors on adherence and the influence of adherence on therapeutic success. This involved a series of investigations.

Initially, the independent influence of various factors on adherence in two diseases studied, i.e. HIV and hypertension, was determined. The factors included disease, age and dosing regimen. A model-based meta-analysis (MBMA) was adopted in this work to allow for multivariate analyses and continuous dependent variables. It was found that (1) although the influence of disease on adherence was significant, it is likely to be of limited clinical significance (2) increased age positively impacts on adherence and (3) the greater frequency of dosing regimens negatively impacts on adherence.

Various measures of adherence were found to be used in the MEMS literature. Despite the advanced ability of MEMS to record patterns of drug taking, percentage of doses taken was the most commonly used measure. Appropriate summary measures of adherence in relation to adherence patterns are suggested in this thesis. These included percentage of days with correct
dosing in conjunction with the number as well as the occurrence of missed doses within a timeframe.

The feasibility of conducting the first MEMS study in New Zealand was undertaken. This study provided suggestions for future MEMS studies in terms of patient identification, recruitment and retention. Collected adherence data were summarised in relation to adherence patterns.

A criterion to quantify the forgiveness of drugs to imperfect adherence was developed. The criterion is described as relative forgiveness (RF). RF is defined as the number of times more likely that target success is attained under perfect adherence compared to imperfect adherence. RF covers the quantification of forgiveness in two scenarios, namely (1) forgiveness of a given drug; and (2) forgiveness between two drugs whose effects can be quantified on the same biomarker of response. Subsequently, RF was illustrated with a hypothetical example and then applied to warfarin as a motivation example. This work was considered at the population level.

The developed relative forgiveness criterion was applied to atorvastatin and omeprazole at the individual patient level. Hence, an individual patient’s clinically observed adherence profile, obtained from the MEMS feasibility study, was used. This study evaluated that RF is generalisable to other drugs of interest. In addition, it can be used at an individual patient level in terms of each patient’s adherence profile. Ultimately, whether or not a drug is forgiving for each patient depends on the individual adherence profile in conjunction with the individual PKPD properties.

In conclusion, better understanding of factors influencing adherence was provided. Adherence data in terms of adherence patterns were described. Ultimately, the time course of drug effects in relation to adherence patterns was quantified. This allows for determining of the forgiveness of drugs under imperfect adherence patterns.
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# GLOSSARY

## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>aPTT</td>
<td>Activated Partial Thromboplastin Time</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike’s information criterion</td>
</tr>
<tr>
<td>BSV</td>
<td>Between subject variability</td>
</tr>
<tr>
<td>C</td>
<td>Category in Chapter 3</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>d</td>
<td>Day</td>
</tr>
<tr>
<td>dL</td>
<td>Decilitre</td>
</tr>
<tr>
<td>FOCE + interaction</td>
<td>First-order conditional estimation with interaction</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-oesophageal reflux disorder</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>H+K+ATPase</td>
<td>Hydrogen potassium adenosine triphosphatase</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>Hydroxyl-3-methylglutaryl coenzyme A</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>i.i.d.</td>
<td>Independent and identically distributed</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>KPD</td>
<td>Kinetic-pharmacodynamic</td>
</tr>
<tr>
<td>L</td>
<td>Litre</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mM</td>
<td>Millimolar</td>
</tr>
<tr>
<td>mmoL</td>
<td>Millimolar</td>
</tr>
<tr>
<td>MBMA</td>
<td>Model-based meta-analysis</td>
</tr>
<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>MPR</td>
<td>Medication possession ratio</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogram</td>
</tr>
<tr>
<td>nM</td>
<td>Nanomolar</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic(s)</td>
</tr>
<tr>
<td>PDC</td>
<td>Proportion of days covered</td>
</tr>
<tr>
<td>PID</td>
<td>Publication identifier</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic(s)</td>
</tr>
<tr>
<td>PKPD</td>
<td>Pharmacokinetic(s)-pharmacodynamic(s)</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised clinical trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>RUV</td>
<td>Residual unexplained variability</td>
</tr>
<tr>
<td>sec</td>
<td>Second</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SID</td>
<td>Study identifier</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
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### VARIABLES & SYMBOLS

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>The amount of drug in a compartment</td>
</tr>
<tr>
<td>$AGE$</td>
<td>Age factor</td>
</tr>
<tr>
<td>$ALAG$</td>
<td>Absorption lag time</td>
</tr>
<tr>
<td>$base$</td>
<td>Baseline aPTT</td>
</tr>
<tr>
<td>$B$</td>
<td>Receptor binding</td>
</tr>
<tr>
<td>$B_{max}$</td>
<td>Maximum binding capacity</td>
</tr>
<tr>
<td>$C$</td>
<td>Concentration</td>
</tr>
<tr>
<td>$C$</td>
<td>Concentration compartment in the lansoprazole PKPD model</td>
</tr>
<tr>
<td>$c_e$</td>
<td>Concentration in the effect compartment</td>
</tr>
<tr>
<td>$C_{50}$</td>
<td>Drug concentration resulting in half maximal effect</td>
</tr>
<tr>
<td>$C1$</td>
<td>Transit chain 1 in the KPD warfarin model</td>
</tr>
<tr>
<td>$C2$</td>
<td>Transit chain 2 in the KPD warfarin model</td>
</tr>
<tr>
<td>$CL$</td>
<td>Clearance</td>
</tr>
<tr>
<td>$CL_m$</td>
<td>$CL$ of the metabolite</td>
</tr>
<tr>
<td>$CL_{mp}$</td>
<td>$CL$ of the metabolite to the parent drug</td>
</tr>
<tr>
<td>$CL_{pm}$</td>
<td>$CL$ of the parent drug (atorvastatin acid) to the metabolite (atorvastatin lactone)</td>
</tr>
<tr>
<td>$\bar{CL}$</td>
<td>$CL$ population average</td>
</tr>
<tr>
<td>$D$</td>
<td>Dose</td>
</tr>
<tr>
<td>$DIS$</td>
<td>Disease factor</td>
</tr>
<tr>
<td>$E$</td>
<td>Effect</td>
</tr>
<tr>
<td>$E$</td>
<td>$\text{H}^+/\text{K}^+\text{-ATPase Enzyme (proton pump) compartment in the lansoprazole PKPD model}$</td>
</tr>
<tr>
<td>$E_0$</td>
<td>Baseline effect</td>
</tr>
<tr>
<td>$E_{max}$</td>
<td>Maximum effect</td>
</tr>
<tr>
<td>$EC_{50}$</td>
<td>Drug concentration resulting in half maximal effect</td>
</tr>
<tr>
<td>$E[g]$</td>
<td>Expected value of $g$</td>
</tr>
<tr>
<td>$fd$</td>
<td>The predefined criteria for the number of successful dose intervals</td>
</tr>
<tr>
<td>$F$</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>$F_{holidays}$</td>
<td>Forgiveness in $F = D - I$</td>
</tr>
<tr>
<td>$F_{missed\ doses}$</td>
<td>The likelihood of drug holidays</td>
</tr>
<tr>
<td>$F_{timing}$</td>
<td>The likelihood of a missed dose</td>
</tr>
<tr>
<td>$F_{timing}$</td>
<td>The form of the bimodal normal distribution for timing pattern errors</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$FI$</td>
<td>Forgiveness index</td>
</tr>
<tr>
<td>$g$</td>
<td>Linear predictor</td>
</tr>
<tr>
<td>$H$</td>
<td>Hydrogen ions (gastric acid) compartment in the lansoprazole PKPD model</td>
</tr>
<tr>
<td>$H^+$</td>
<td>Hydrogen ions</td>
</tr>
<tr>
<td>$i$</td>
<td>Index for an individual (patient)</td>
</tr>
<tr>
<td>$I$</td>
<td>Index for a study for the MBMA work</td>
</tr>
<tr>
<td>$I$</td>
<td>Dose interval in $F = D - I$</td>
</tr>
<tr>
<td>$I_{max}$</td>
<td>Maximum degree of inhibition</td>
</tr>
<tr>
<td>$INR_{BASE}$</td>
<td>Baseline INR</td>
</tr>
<tr>
<td>$INR_{max}$</td>
<td>Maximum INR</td>
</tr>
<tr>
<td>$j$</td>
<td>Index for an observation for the $i$th individual</td>
</tr>
<tr>
<td>$k$</td>
<td>First-order elimination rate constant</td>
</tr>
<tr>
<td>$k_a$</td>
<td>First-order absorption rate constant</td>
</tr>
<tr>
<td>$k_d$</td>
<td>Dissociation rate constant</td>
</tr>
<tr>
<td>$k_{deg}$</td>
<td>First elimination rate constant of proton pumps in the lansoprazole PKPD model</td>
</tr>
<tr>
<td>$k_{deg}$</td>
<td>Second elimination rate constant of proton pumps</td>
</tr>
<tr>
<td>$k_e$</td>
<td>First-order elimination rate constant</td>
</tr>
<tr>
<td>$k_{eq}$</td>
<td>Equilibrium rate constant</td>
</tr>
<tr>
<td>$k_m$</td>
<td>Mean acid production rate</td>
</tr>
<tr>
<td>$k_{off}$</td>
<td>Rate of disassociation of a drug receptor complex</td>
</tr>
<tr>
<td>$k_{on}$</td>
<td>Rate of formation of a drug receptor complex</td>
</tr>
<tr>
<td>$k_{out}$</td>
<td>First-order elimination rate constant for $I$</td>
</tr>
<tr>
<td>$ln$</td>
<td>Natural logarithm</td>
</tr>
<tr>
<td>$MTT$</td>
<td>Mean transit time</td>
</tr>
<tr>
<td>$N_{missed \ doses}$</td>
<td>The total number of missed doses</td>
</tr>
<tr>
<td>$OH^-$</td>
<td>Hydroxide ions</td>
</tr>
<tr>
<td>$p$</td>
<td>The probability of an actual dosing time being in the first normal distribution</td>
</tr>
<tr>
<td>$P$</td>
<td>Probability in the Markov probability transition matrix</td>
</tr>
<tr>
<td>$P_{p}$</td>
<td>Probability of success for either perfect adherence ($P_p$) or imperfect adherence imperfect adherence ($P_{ip}$)</td>
</tr>
<tr>
<td>$P_{ip}$</td>
<td>The probability of successful attainment of a treatment target under imperfect adherence</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$P_{Markov}$</td>
<td>The Markov probability transition matrix</td>
</tr>
<tr>
<td>$P_p$</td>
<td>The probability of successful attainment of a treatment target under perfect adherence</td>
</tr>
<tr>
<td>$Q$</td>
<td>Intercompartmental clearance of the parent drug</td>
</tr>
<tr>
<td>$R_{in}$</td>
<td>Rate of production/input</td>
</tr>
<tr>
<td>$RF$</td>
<td>Relative forgiveness</td>
</tr>
<tr>
<td>$REG$</td>
<td>Regimen factor</td>
</tr>
<tr>
<td>$s$</td>
<td>Successful attainment of a treatment target</td>
</tr>
<tr>
<td>$slope$</td>
<td>Slope in a combination of a linear and an $E_{max}$ model for aPTT</td>
</tr>
<tr>
<td>$S$</td>
<td>Overall success for a patients dosing regimen</td>
</tr>
<tr>
<td>$S_{max}$</td>
<td>Maximum degree of stimulation</td>
</tr>
<tr>
<td>$t$</td>
<td>Time</td>
</tr>
<tr>
<td>$t_{lag}$</td>
<td>Absorption lag time</td>
</tr>
<tr>
<td>$TTR_i$</td>
<td>The proportion of dose intervals within the therapeutic range for the $i$th individual</td>
</tr>
<tr>
<td>$V$</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>$V_1$</td>
<td>$V$ of the parent drug in the central compartment</td>
</tr>
<tr>
<td>$V_2$</td>
<td>$V$ of the parent drug in the peripheral compartment</td>
</tr>
<tr>
<td>$V_3$</td>
<td>$V$ of the metabolite</td>
</tr>
<tr>
<td>$y$</td>
<td>Observation/dependent variable</td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>Intercept in the linear predictor $g$</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Factor coefficient: specifically, disease coefficient in the MBMA work</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Age coefficient</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>Dosing regimen coefficient</td>
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<tr>
<td>$\varepsilon$</td>
<td>Residual unexplained variability</td>
</tr>
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<td>$\gamma$</td>
<td>Hill coefficient</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Mean</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Between subject/study random effect</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>The expected rate of missed doses for a dose period</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>Variance of residual unexplained variability</td>
</tr>
<tr>
<td>$\omega^2$</td>
<td>Variance of between subject/study variability</td>
</tr>
</tbody>
</table>
STRUCTURE OF THE THESIS

The overarching aim of this thesis was to quantify adherence, influences of factors on adherence and the influence of adherence on therapeutic success. The thesis is divided into seven chapters and appendices (see Table P.1).

Chapter 1 provides an introduction to adherence and pharmacokinetics-pharmacodynamics. Background information on adherence including its impact on clinical outcomes and interventions to improve adherence is summarised. This leads to a view of quantifying adherence with respect to adherence patterns. The association between adherence and the time course of drug effects is then explained.

Chapter 2 presents the independent influence of various factors on adherence in two diseases. A model-based meta-analysis technique was used here to provide a better understanding of factors influencing adherence in terms of multivariate analyses and continuous dependent variables.

Chapter 3 includes the investigation of a variety of measures of adherence used in a subset of Medication Event Monitoring System (MEMS) literature. Appropriate measures of adherence were suggested over the percentage of prescribed doses taken.

Chapter 4 includes the feasibility of conducting the first MEMS study in New Zealand in terms of patient identification, recruitment and retention. In addition, collected adherence data were presented in terms of adherence patterns.

Chapter 5 focuses on the quantification of the forgiveness on drugs to imperfect adherence. This work involved the development of a criterion to quantify forgiveness; the illustration of the criterion for a theoretical example; and the evaluation of the forgiveness of warfarin as a motivating example.

Chapter 6 presents the application of the developed forgiveness to atorvastatin and omeprazole. An individual patient’s clinically observed adherence profile was used in this chapter.
Chapter 7 concludes the thesis with a discussion of the findings of each chapter and future prospects.

Appendices consist of additional material related to the individual chapters including MATLAB code®.

Table P.1: Structure of this thesis

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 1</td>
<td>Introduction</td>
</tr>
<tr>
<td>Chapter 2</td>
<td>A model-based meta-analysis of the influence of factors that impact on adherence</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>Measures of adherence in the Medication Event Monitoring System literature</td>
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<tr>
<td>Chapter 4</td>
<td>A Medication Event Monitoring System feasibility study in New Zealand</td>
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<tr>
<td>Chapter 5</td>
<td>Quantification of the forgiveness of drugs to imperfect adherence</td>
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<td>Chapter 6</td>
<td>Application of relative forgiveness using clinically observed adherence profiles</td>
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<tr>
<td>Chapter 7</td>
<td>Discussion and future prospects</td>
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<tr>
<td>Appendices</td>
<td>Appendix to Chapter 2</td>
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<td>Appendix to Chapter 4</td>
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<td>Appendix to Chapter 5</td>
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<td>Appendix to Chapter 6</td>
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</tbody>
</table>

For Chapters 2 and 5 from which publications have arisen, I was the main contributor to these chapters. My contributions included writing the manuscript, designing and performing the research, and analysing the data.
Chapter 1: Introduction
This introduction is divided into four main sections. It begins with adherence, impact on clinical outcomes and attempts to improve adherence. The second section is related to quantifying adherence. This section covers the epistemology of non-adherence in aspect of failure to initiate treatment, suboptimal implementation and early discontinuation. Measurement of adherence including electronic monitoring as well as deviation from perfect adherence are then presented. The third section discusses the association between adherence and the time course of drug effects. This section involves pharmacokinetics-pharmacodynamics, heterogeneity and uncertainty as well as the illustration of the impact of imperfect adherence on the time course of drug effects. Lastly, choices of drugs as an alternative to assist patients with suboptimal adherence are discussed. These include drugs and dosing regimens that are associated with greater adherence and drugs that are forgiving. The fourth section outlines the aims of this thesis.

1.1. Adherence, impact on clinical outcomes and attempts to improve adherence

1.1.1. Describing and defining medication taking behaviour

The importance of medication taking behaviour has long been recognised. Hippocrates in 400 BC stated that “[The physician] should keep aware of the fact that patients often lie when they state that they have taken certain medicines.”[1]. The emphasis was noted by the quote of the former Surgeon General, C. Everett Koop in 1984 “Drugs don’t work in patients who don’t take them.”[2]. There have been many attempts to describe medication taking behaviour. According to the article of Vrijens et al. in 2012 [3] which summarised the history of terms used to describe medication taking behaviour, it appeared that, from 1976 to 2009 there were three commonly used terms which were compliance, adherence and concordance with a trend of change from compliance to adherence in recent years [3].

The term patient compliance first became a Medical Subject Heading (MeSH) search term in 1975 [4] and was defined by the US National Library of
Medicine as “voluntary cooperation of the patients in following a prescribed regimen.”[5]. Compliance was also defined in several other ways [3, 6] with the most cited one [3] defined by Sackett & Haynes in 1976 as “the extent to which the patient’s behaviour (in terms of taking medications, following diets or executing other lifestyle changes) coincides with the clinical prescription.”[7]. Compliance holds negative connotations in that patients passively obey physician’s instructions rather than follow an agreed treatment plan [3, 8, 9], i.e. a plan that was agreed by both patient and prescriber.

It was recognised that, from 1975 to 1980, there was debate whether to use the term compliance or adherence in research [10]. Adherence was not frequently or clearly defined at that time but according to The Random House college dictionary in 1975, it referred to “fidelity or sticking fast to something or holding closely or firmly to something, as to a plan; it may also refer to being consistent.”[11].

The shift from the term compliance to adherence seemed to occur in 1993 although adherence did not become a MeSH term until 2008 [3, 4]. In 2003, the World Health Organisation (WHO) defined adherence as “the extent to which a person’s behaviour – taking medications, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider.”[12]. The definition of adherence hence appears to reduce the power of physicians on patients and implies cooperation between them.

With respect to the term concordance, this was also proposed to replace compliance by the Royal Pharmaceutical Society of Great Britain in 1995 [3, 9]. It was defined as “an agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, when and how their medicine is taken.”[13]. Both adherence and concordance seem to share similarities in terms of mutual agreement of treatment plans with the preference of adherence over concordance in research. Although the definitions have been established, adherence and compliance have still occasionally been used interchangeably. Compliance seems to be in favour among some researchers regarding quantitative
components of medication taking behaviour, for example, time course of drug effects associated with medication taking behaviour. However, over the years, adherence has appeared to be increasingly used in this quantitative type of research to be consistent in the literature. Hence, in this thesis, adherence is the selected term used.

It was acknowledged that the inconsistency of the use of terms in research into adherence could impede the interpretation and comparison of findings across study areas. In addition, the previously available taxonomy was insufficient to provide quantitative understanding of adherence e.g. what time is each dose taken? [3]. This led to a group of researchers working on establishing a new taxonomy of adherence. This work started with performing a systematic literature review in 2009. A final consensus meeting was held in 2010. Subsequently, the taxonomy was first presented at the European Society for Patient Adherence, Compliance and Persistence meeting, Poland, 2010. In 2012, the taxonomy was proposed by Vrijens et al. [3]. Adherence is defined as “the process by which patients take their medications as prescribed.” [3]. The authors proposed that adherence is the process of the three components, namely 1) initiation, 2) implementation and 3) discontinuation. These three components are described in Table 1.1. Note that in this thesis, the term drugs and medications may be used interchangeably.

**Table 1.1: Explanation of each component of adherence [3]**

<table>
<thead>
<tr>
<th>Component</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>starts “when the patient takes the first dose of a prescribed medication”</td>
</tr>
<tr>
<td>Implementation</td>
<td>is “the extent to which a patient’s actual dosing [regimen] corresponds to the prescribed dosing regimen, from initiation until the last dose”</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>happens “when the patient stops taking the prescribed medications, for whatever reason(s)”</td>
</tr>
</tbody>
</table>

Persistence denotes the duration between initiation and the last dose taken prior to discontinuation [3].
It is, however, important to note that the entire adherence process may be broader i.e. ranging from patients making the decision to see a physician when appropriately needed, through to attending a clinic for subsequent follow-ups and prescriptions. Therefore, it depends on the purpose of the individual researcher to determine the scope of adherence process studied. Further discussion with respect to failure to initiate treatment to early discontinuation is provided in section 1.2.1. For the purpose of this thesis, adherence is viewed from initiation to discontinuation with a focus on implementation. In addition, adherence is viewed in terms of medication adherence where lifestyle modification is not considered.

1.1.2. Association between adherence and clinical outcomes

A summary of key meta-analyses and/or systematic reviews investigating the association between adherence and clinical outcomes is presented in Table 1.2. Six studies are summarised. Studies were selected based on the study type of meta-analyses and/or systematic reviews. Studies related to interventions to improve adherence were excluded. Therapeutic areas were broad including hypertension, diabetes, hyperlipidaemia, HIV, cancer, cardiovascular disease and coronary heart disease. A variety of methods to monitor adherence were employed including pill counts, self-reports, prescription refill records, electronic monitoring and drug plasma concentrations. Commonly used adherence measures included criteria such as the percentage of drugs taken e.g. $\geq 70\%$, $\geq 80\%$ and $\geq 90\%$ of various methods including pill counts, prescription refill records, self-reports, clinician estimates and electronic monitoring. Adherence aspects considered varied and included adherence to medications; adherence to non-medications; adherence to beneficial and harmful therapy; and adherence to placebo. The study of Simpson et al. [14] explored adherence to harmful therapy. The authors stated that two studies reported the increased risk of mortality with active drug therapy compared to placebo and hence were defined as harmful therapy [14]. The study of Yue et al. [15] specifically looked at adherence to placebo.
Overall, these meta-analyses and/or systematic reviews have shown that increased adherence results in lower mortality. Increased adherence also decreases the risk of developing cardiovascular disease including patients prescribed statins and antihypertensive drugs. In contrast, poor adherence contributed to higher mortality and/or the risk of developing cardiovascular disease. Interestingly, increased adherence to placebo was associated with lower mortality. It may be plausible that patients with good adherence to placebo may be in general “healthy adherers”, which refers to patients with overall healthy behaviour including beneficial therapy and life style changes [14, 15]. The finding of increased adherence to harmful therapy in the study of Simpson et al. showed the association between this and higher mortality [14]. Adherence to harmful therapy may occur in patients with good adherence, who respond to drugs differently from patients on average, and therefore develop adverse drug effects [14].

Table 1.2: A summary of the association between adherence and clinical outcomes

<table>
<thead>
<tr>
<th>Authors/year/type of the paper</th>
<th>No. of studies (years)</th>
<th>Study design (no. of studies)</th>
<th>Total no. of patients</th>
<th>Therapeutic areas (no. of studies) identified as per the paper</th>
<th>Methods to monitor adherence</th>
<th>Adherence measures</th>
<th>Adherence aspects considered in the paper</th>
<th>Clinical outcome measures in the paper</th>
<th>Results</th>
</tr>
</thead>
</table>
- Diabetes (5)  
- Heart disease (7)  
- Hypercholesterolaemia (7)  
- Hypertension (6)  
- Intestinal disease (5)  
- Otitis media (6)  
- Sleep apnea (5)  
- Transplant (5)  
- Eye disorders (4)  
- Ulcers (3) | Included pill counts, self-reports, pharmacy records, medical records, parent reports, serum assays, urine assays, electronic monitoring, dietician reports | - Various “continuous” measures e.g. percentage of prescribed doses taken (“continuous” defined by the authors including a measure with three or more ordered response categories) | 1) Adherence to medications  
2) Adherence to non-medications e.g. exercise, diet, behavioural interventions | “Better” treatment outcomes based on positive effect sizes | - Standardised risk difference: Adherence decreased the risk for a null or poor treatment outcomes by 26%. - Standardised odds ratio: The odds of good outcomes was three times higher in adherers compared to
<table>
<thead>
<tr>
<th>Authors/year/type of the paper</th>
<th>No. of studies (years)</th>
<th>Study design (no. of studies)</th>
<th>Total no. of patients</th>
<th>Therapeutic areas (no. of studies) identified as per the paper</th>
<th>Methods to monitor adherence</th>
<th>Adherence measures</th>
<th>Adherence aspects considered in the paper</th>
<th>Clinical outcome measures in the paper</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiMatteo et al. 2002 [16] meta-analysis (continued)</td>
<td>- Venous disease (3) - Arthritis (2)</td>
<td>- Various dichotomous measures e.g. adherence ≥ 70%, 75%, 80%, 85%, 90%</td>
<td></td>
<td>non-adherers.</td>
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<tr>
<td>Simpson et al. 2006 [14] meta-analysis</td>
<td>21 (1971-2005) - RCT (8) - Cohort: 9146 - RCT: 37701 - Treatment arm: 18068 - Placebo arm: 19633</td>
<td>- Post-myocardial infarction management (8) - HIV (7) - Primary prevention of cardiovascular disease (2) - Type 2 diabetes (1) - Hypercholesterolaemia (1) - Heart failure (1) - Heart transplant (1)</td>
<td>46847 Total: 847 - Cohort: 9146 - RCT: 37701 - Treatment arm: 18068 - Placebo arm: 19633</td>
<td>Pill counts, clinician’s impression, pharmacy refills, self-reports, frequency of clinic visits, Medication Event Monitoring System, thromboxane concentration, drug plasma concentration</td>
<td>Good adherence: - % of adherence reported from each study ≥66%, ≥75%, ≥80% - Others - No missed dose in previous 48 hours - No variation in dose compliance and no drug holidays - Continued use - Less than healthy volunteer - Collection of new tablet supply - Ongoing attendance at clinic - Therapeutic range</td>
<td>1) Adherence to placebo 2) Adherence to harmful drug therapy (The authors stated that two studies reported the increased risk of mortality with active drug therapy compared to placebo) 3) Adherence to beneficial drug therapy</td>
<td>1) Good adherence to beneficial therapy significantly lowered mortality rate (odds ratio = 0.55, CI = [0.49, 0.62], p&lt;0.0001). 2) Good adherence to harmful therapy significantly increased mortality rate (odds ratio = 2.90, CI = [1.04, 8.11], p=0.04). 3) Good adherence to placebo also significantly lowered mortality rate (odds ratio = 0.56, CI = [0.43, 0.74], p&lt;0.0001).</td>
<td></td>
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<tr>
<td>Authors/year/type of the paper</td>
<td>No. of studies (years)</td>
<td>Study design (no. of studies)</td>
<td>Total no. of patients</td>
<td>Therapeutic areas (no. of studies) identified as per the paper</td>
<td>Methods to monitor adherence</td>
<td>Adherence measures</td>
<td>Adherence aspects considered in the paper</td>
<td>Clinical outcome measures in the paper</td>
<td>Results</td>
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<tr>
<td>Chowdhury et al. 2013 [17]</td>
<td>44 (years search: 1960-2012)</td>
<td>- Cohort (33) - Nested case-control (8) - Clinical trial (3)</td>
<td>Total: 1978919 - Cohort: 1721351 - Nested case-control: 222160 - Clinical trial: 35408</td>
<td>Cardiovascular disease</td>
<td>Medication possession ratio* (MPR), proportion of days covered* (PDC), self-reports, Medication Event Monitoring System, blood tests and other indirect methods</td>
<td>Good adherence: % of adherence ≥ 80%</td>
<td>Adherence to cardiovascular drugs e.g. statins, antihypertensive drugs, aspirin and others</td>
<td>1) Risk estimates for cardiovascular disease 2) Risk estimates for mortality</td>
<td>1) Relative risks (95% CI) for developing cardiovascular disease in good compared to poor adherence: - Any drugs: 0.80 (0.77–0.84) - Statins: 0.85 (0.81–0.89) - Antihypertensive drugs: 0.81 (0.76–0.86) - Aspirin: 0.60 (0.31–1.16)* 2) Relative risks (95% CI) for mortality in good compared to poor adherence: - Any drugs: 0.62 (0.57–0.67) - Statins: 0.55 (0.46–0.67) - Antihypertensive drugs: 0.71 (0.64–0.78) - Aspirin: 0.45 (0.16–1.29)*</td>
</tr>
<tr>
<td>Authors/ year/type of the paper</td>
<td>No. of studies (years)</td>
<td>Study design (no. of studies)</td>
<td>Total no. of patients</td>
<td>Therapeutic areas (no. of studies) identified as per the paper</td>
<td>Methods to monitor adherence</td>
<td>Adherence measures</td>
<td>Adherence aspects considered in the paper</td>
<td>Clinical outcome measures in the paper</td>
<td>Results</td>
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<tr>
<td>De Vera et al. 2014 systematic review</td>
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<tr>
<td>Hood et al. 2009 [19] meta-analysis</td>
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<td></td>
</tr>
<tr>
<td>21 (1990-2008)</td>
<td>Not categorised in this paper</td>
<td>Total: 2492</td>
<td>Paediatric type 1 diabetes</td>
<td>Blood glucose monitoring, survey</td>
<td>No good adherence defined</td>
<td>Association between adherence and haemoglobin A1c</td>
<td>Glycaemic control</td>
<td>A mean effect size was -0.28 (95% CI -0.32 to -0.24) indicating that as adherence increased, haemoglobin A1c values decreased.</td>
<td></td>
</tr>
<tr>
<td>Authors/year/type of the paper</td>
<td>No. of studies (years)</td>
<td>Study design (no. of studies)</td>
<td>Total no. of patients</td>
<td>Therapeutic areas (no. of studies) identified as per the paper</td>
<td>Methods to monitor adherence</td>
<td>Adherence measures</td>
<td>Adherence aspects considered in the paper</td>
<td>Clinical outcome measures in the paper</td>
<td>Results</td>
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<tr>
<td>Yue et al. 2014 [15] meta-analysis</td>
<td>8 (1980-2005)</td>
<td>Not categorised in this paper</td>
<td>44711</td>
<td>Chronic heart failure, cardiovascular disease, hyperlipidaemia, arrhythmia, myocardial infarction, coronary heart disease</td>
<td>Pill counts, self-reports, clinician estimates</td>
<td>Good adherence: % of adherence &gt;66%, &gt;70%, &gt;75%, &gt;80%, 95%</td>
<td>The effect of placebo adherence on decreasing cardiovascular mortality</td>
<td>Cardiovascular mortality</td>
<td>Good adherence to placebo resulted in decreased cardiovascular mortality (odds ratio = 0.68, 95% CI = 0.60-0.77).</td>
</tr>
</tbody>
</table>

* Three studies were included.

* MPR (medication possession ratio) is “the percentage of days exposed to medication in a given follow-up period calculated from the start of prescription until the date of the outcome for cases and date of selection for controls” [18].

* PDC (proportion of days covered) is calculated from “the number of days of medication dispensed divided by the number of days over which the prescriptions were used” [18].
1.1.3. Understanding non-adherence and existing solutions

1.1.3.1. Understanding non-adherence

1.1.3.1.1. Intentional and unintentional non-adherence

First, perfect adherence can be defined as the patient takes drugs exactly as prescribed i.e. the patient follows the nominal regimen. Non-adherence may occur due to many reasons. To better understand the reasons, non-adherence can be viewed as either intentional or unintentional non-adherence [20, 21].

Intentional non-adherence refers to patients who decide not to follow the nominal dosing regimen deliberately. This includes skipping, altering, delaying and stopping the nominal dosing regimen [20, 22, 23]. In contrast, unintentional non-adherence refers to accidental errors of patients in following the nominal regimen which is mainly driven by forgetfulness [20, 22, 23].

It was demonstrated that patients’ beliefs about drugs with respect to necessity (i.e. pros/ reasons for taking drugs) and concerns (i.e. cons/ reasons against taking drugs) were associated with intentional adherence [20, 22, 24]. In the HIV study of Wroe and Thomas, necessity of taking drugs included to maintain health as well as quality of life, to increase life expectancy, to respond to feedback from blood tests [24]. Concerns of taking drugs may involve side effects, the perspective of potential side effects, interruption of lifestyle e.g. diuretics and feeling that already taking too many doses [22, 24].

To quantify patients’ beliefs about drugs, the decision balance of the proportion of pros and that of cons was proposed as follows \([\text{pros}/(\text{pros} + \text{cons})] - [\text{cons}/(\text{pros} + \text{cons})]\) [20, 24]. This formula can be simplified as \((\text{pros} - \text{cons})/(\text{pros} + \text{cons})\) where values lie between -1 and 1 [20, 24]. It was suggested that emotional status e.g. depression as well as cost barriers may contribute to intentional non-adherence [23-26].

Unintentional non-adherence may be related to patient characteristics e.g. age and complexity of dosing regimen [20, 21, 24]. However, intentional and unintentional non-adherence may overlap since patients who view a low necessity of taking drugs
may tend to forget to take them [23, 27]. In addition, an individual patient may experience both intentional and unintentional non-adherence [22, 23].

Studies with respect to intentional and unintentional non-adherence have been undertaken in various therapeutic areas including HIV, kidney transplantation, asthma, acute coronary syndrome and a variety of diseases [20, 22-24, 28, 29]. Overall, the findings have shown that the proportion of patients with unintentional non-adherence was greater than those with intentional non-adherence. In a survey of 24,017 patients with asthma, hypertension, diabetes, hyperlipidaemia, osteoporosis and depression, Gadhari and McHorney [28] found that approximately 70% of patients reported unintentional non-adherence at least once over the six months. Of these, 62% forgot to take medications at least once; 37% had experienced shortage of medications; and 23% reported being careless about taking medications on schedule. Around 34% of patients reported intentional non-adherence at least once over the six months. Of these, the most common reason was suboptimal implementation to make medications last longer with 18% and 15% reporting missing doses and reducing doses, respectively, a further 14% of the patients altered doses to suit their own needs [28]. One of the possible explanations of patients making current medications last longer than appropriate prescriptions may be due to cost barriers. These include medication and transportation costs leading to a failure to pick up, a failure to continue to refill, or to refill their prescriptions on schedule [25, 26].

1.1.3.1.2. Factors influencing adherence

In the previous section, some possible factors underlying intentional and unintentional non-adherence were introduced. However, it appears that the factors may be broader. In 1979, it was proposed that there were more than 200 factors influencing adherence [30]. WHO in 2003 recommended that factors influencing adherence may be categorised into five dimensions, namely (1) socioeconomic related factors, (2) healthcare team and system related factors, (3) condition related factors, (4) therapy related factors and (5) patient related factors [12]. In 2013, a review of systematic reviews of Kardas et al. [31] identified
an overall of 771 individual factor items. This study was built on the WHO work, the authors suggested that previous work did not consider the influence of factors on adherence with respect to the three components of adherence, namely initiation, implementation and discontinuation as well as persistence [31]. In this study of Kardas et al., factors were reviewed and grouped into the five dimensions. Each dimension consists of a number of clusters as shown in Table 1.3. This classification provides a clearer perspective on a variety of elements under each dimension. This study also considered treatment duration in terms of acute and chronic diseases as well as direction of the influence of factors on adherence (i.e. positive, negative or neutral influence). It was concluded that non-adherence was influenced by multiple factors [31]. For further details about the direction of the influence of each factor on adherence, see [31].

**Table 1.3: Dimensions of factors influencing adherence with different clusters [31]**

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Number of clusters</th>
<th>Details of each cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Socioeconomic related factors</td>
<td>8 clusters</td>
<td>Family support, family/caregivers factors, social support, social stigma of a disease, costs of drugs and/or treatment, prescription coverage, socioeconomic status, employment status</td>
</tr>
<tr>
<td>(2) Healthcare team and system related factors</td>
<td>6 clusters</td>
<td>Barriers to healthcare, drug supply, prescription by a specialist, information about drug administration, healthcare provider-patient communication and relationship, follow-up</td>
</tr>
<tr>
<td>(3) Condition related factors</td>
<td>6 clusters</td>
<td>Presence of symptoms, disease severity, clinical improvement, psychiatric condition, certain diagnoses/indications, duration of the disease</td>
</tr>
<tr>
<td>(4) Therapy related factors</td>
<td>6 clusters</td>
<td>Adverse effects, patient friendliness of the regimen, drug effectiveness, duration of the treatment, drug type, well organised treatment</td>
</tr>
</tbody>
</table>
### Dimension | Number of clusters | Details of each cluster
---|---|---
(5) Patient related factors* | 14 clusters | Age, gender, marital status, education, ethnicity, housing, cognitive function, forgetfulness and reminders, knowledge, health beliefs, psychological profile, comorbidities and patient history, alcohol or substance abuse, patient-related barriers to adherence

* This study included demographic variables e.g. age under the patient related factors. Previously, the work of WHO [12] considered demographic variables under the socioeconomic related factors.

Despite this intensive review, the influence of factors that impact adherence can be better understood when a continuous dependent variable e.g. percentage of adherence and multiple factors are concurrently taken into account. This approach was explored using a model-based meta-analysis technique in Chapter 2.

Understanding these factors leads to designing appropriate interventions to enhance adherence. It appears that the area of healthcare team and system related factors has been least studied and much intervention research has focused on the patient level [32].

#### 1.1.3.2. Existing solutions for non-adherence

Many methods have been developed to enhance adherence. It should be noted that all methods are based on the premise that the current medications are optimal and immutable; and also that patients have medications at hand. Interventions have been grouped into various perspectives in the literature [8, 33-36]. According to the review of van Dulmen et al., interventions may be categorised into technical, behavioural, educational and multifaceted interventions [34]. Some examples of each intervention are given in Table 1.4 [34]. Note that certain interventions exist though may not lie in a particular category such as those to increase access by decreasing barriers to medications.
Chapter 1: Introduction

Table 1.4: Some examples of each intervention [34]

<table>
<thead>
<tr>
<th>Type of interventions</th>
<th>Some examples</th>
</tr>
</thead>
</table>
| Technical             | - Reducing the frequency and/or number of medications  
  - The use of blister packs |
| Behavioural           | - The use of reminders, memory aids including phone, computer, mail and home visits  
  - Monitoring approaches including diaries, calendars  
  - Providing patients with support, feedback |
| Educational           | - Individualised or group education  
  - Written, audio, visual education  
  - Face to face contact |
| Multifaceted          | - Combinations of above interventions |

Another classification of interventions may be viewed as 8 categories according to the review of Demonceau et al. (Table 1.5) [36], which considered a taxonomy developed in previous research [33, 37-39]. This classification partly overlaps with Table 1.4 [34].

Table 1.5: Another classification of interventions [36]

<table>
<thead>
<tr>
<th>Type of interventions</th>
<th>Details</th>
</tr>
</thead>
</table>
| 1. Interventions based on a treatment simplification | - Change in dosing regimen  
  - Change in formulation |
| 2. Cognitive-educational interventions*              | - Individualised or group setting  
  - Verbal, written, audio, visual approaches  
  - To educate and motivate patients |
| 3. Behavioural-counselling interventions*            | - Pillboxes, calendars, reminders, skills building by health care providers, problem solving  
  - To reinforce and empower patients |
| 4. Social-psycho-affective interventions*            | - Family counselling, peer group meetings, stress management  
  - To focus on patients’ feelings, social relationship and support |
There has been much intervention research targeting the patient level e.g. as seen in meta-analyses and/or systematic reviews [33, 36, 37, 40-44]. Here, major studies will be discussed, namely the most recently revised Cochrane systematic review [42] and a 2013 systematic review and meta-analysis by Demonceau et al. [36].

It has been demonstrated that although interventions can enhance adherence, the effect may not last after the intervention ceases. The following indicative study of Lee et al. [45] describes this situation, which was reiterated in the study of Demonceau et al. Lee et al. found an increase in adherence among patients with hypertension and hyperlipidaemia after an intervention phase for six months (from 61.2% to 96.9%, measured by pill counts) [45]. Intervention strategies included individualised medication education (educational/cognitive interventions), the use of blister packs (counselling/behavioural interventions) and follow-up visits with pharmacists every two months (psychological/affective interventions). Significant reductions in systolic blood pressure and low-density lipoprotein (LDL) were observed. The patients were later randomised into either a usual care group or a continued intervention group for another six months. During this phase, systolic blood pressure was significantly
reduced between study groups but the reduction in LDL was not significant. The usual care group adherence dramatically dropped to 69.1% whereas adherence was sustained in the continued intervention group (95.5%) [45].

The Cochrane systematic review was recently revised in 2008 [42]. In this review, the duration of long term treatments was defined as a minimum of a six month follow-up. Included studies were those that assessed both adherence improvement and the impact of improved adherence on treatment outcomes. Sixty nine randomised clinical trials (RCTs) and 9 RCTs were included for long term treatments and short term treatments, respectively. For short term treatments, it was found that a total of 10 interventions were implemented in the 9 RCTs. Of these, 40% of the interventions enhanced adherence and also at least one treatment outcome, where more than one treatment outcomes may be measured. The four effective interventions fell into educational/cognitive (n=1), counselling/behavioural (n=2) and psychological/affective interventions (n=1). The improved treatment outcomes were Helicobacter pylori eradication and lower occurrence of asthma in patients with seasonal allergic rhinitis. However, 1 intervention in 1 RCT (10% of the interventions) demonstrated a significant improvement in adherence but not significant impact on treatment outcomes. It was suggested that the trials were generally small [42].

With regards to long term treatments, of 83 interventions implemented in 70 RCTs, around 43% of the interventions were reported to significantly improve adherence [42]. However, only around 30% of the interventions showed significant improvement of at least one treatment outcome. The authors noted that one possible reason for not detecting the influence of improved adherence on treatment outcomes may be due to the low power of sample sizes in many recruited studies. It was suggested that each intervention and control arm should have at least 60 participants. It has been found that for long term treatments, nearly all effective interventions were multifaceted. Interventions consisted of combinations including more convenient care, reminders, telephone follow-up, self-monitoring, counselling, information, reinforcement, family therapy, psychological therapy, crisis intervention and supportive care [42]. The authors
also concluded that dosing regimen simplification can enhance both adherence and treatment outcomes [42].

A more recent systematic review and meta-analysis by Demonceau et al. was published in 2013 [36]. Seventy-nine RCTs were included where adherence was assessed by electronic monitoring. Feedback from recent dosing patterns obtained from electronic monitoring and educational/cognitive interventions were reported to have significant impact on adherence (multivariate model: 8.8% and 5% of adherence improvement, \( p<0.01 \) and \( p=0.02 \), respectively; univariate models: 19.8% and 16.1% of adherence improvement, \( p<0.01 \) and \( p=0.04 \), respectively compared to studies not including such an intervention). The findings of this study were in-line with the study of Kripalani et al. where it was found that dosing regimen simplification and repeated adherence assessment with feedback were the most common and effective types of interventions [33].

In addition, this work found that the effect of the interventions did not persist with a loss of percentage of adherence by 1.1% each additional month (\( p<0.01 \)). However, of 57 studies which also assessed treatment outcomes, only 8 studies indicated the link between improved adherence and treatment outcomes [36]. Although the results of educational/cognitive interventions were found to be significant in this current study, Conn et al. found that education alone did not effectively enhance adherence [43]. There was also evidence that counselling/behavioural and psychological/affective interventions were more effective with respect to promoting behavioural changes in long term [46]. A recent expert review by Vrijens et al. (2014) proposed a possible combination of effective interventions which comprises three elements: 1) education (to increase knowledge), 2) motivation (to increase self-efficacy) and 3) electronic monitoring measurement to provide patients with feedback (to increase awareness) [47].

To move forward on effective interventions to enhance adherence, it has been proposed that it is not sufficient to solely focus on the patient level. Future intervention research should look at multi-level interventions comprising 1) patient level, 2) provider level (also termed micro level) including communication styles with patients, behavioural change management
competencies, 3) organisation of care processes level (termed meso level) including care continuity, routine behavioural assessments at follow-ups, and 4) health care system level (termed macro level) including medication coverage [32, 48]. In addition, it was suggested that interventions should be considered at the level of each component: initiation, implementation and discontinuation [47].

1.2. Quantifying adherence

1.2.1. Overview of epistemology of non-adherence

The epistemology of non-adherence is presented for failure to initiate treatment, suboptimal implementation and early discontinuation.

1.2.1.1. Failure to initiate treatment

Here, failure to initiate treatment includes a broader range of mechanisms beyond the process of adherence. The phenomenon that “much ill health does not reach medical attention.” is defined as the “illness iceberg” in 1963 [49]. Hannay in 1980 described the term “symptom iceberg” based on people’s perceptions of symptoms with corresponding referral behaviour, as follows “a symptom was defined as part of the medical iceberg if the referral was none or late, when either the pain or disability was severe, or the symptom was considered to be serious.” [50]. In 2011, Elliott et al. revisited the symptom iceberg in the UK population after primary care changes were introduced [51]. Symptoms were classified into level 1 (least serious) to level 5 (most serious) after the authors received feedback from general practitioners. Level 1 symptoms include difficulty sleeping, cold or flu and diarrhoea where joint pain, indigestion/heartburn and wheezy chest are examples of level 3 symptoms; and level 5 symptoms include chest pain and coughing up blood. The results showed that regardless of the severity of symptoms ranging from level 1 to 5, around half of patients did nothing and left their symptoms untreated for 2 weeks [51]. The authors commented that the 2 week period was chosen since it seemed sufficient to allow many symptoms to develop to their full course leading to corresponding actions [51].
A part of failure to initiate treatment that is related to non-adherence may be viewed beyond the point that a patient experiences a symptom and further seeks help from clinicians but fails to initiate prescribed medications. The mechanisms may include 1) a failure to pick up prescribed medications and 2) a failure to start the first dose of prescribed medications given that medications are available to patients.

A failure to pick up prescribed medications has been termed primary non-adherence. The occurrence of primary non-adherence reported by Raebel et al. was 7% in the group of patients with hypertension, diabetes and hyperlipidaemia [52]. However, the study of Fischer et al. has found a higher rate of primary non-adherence of around 20% with the same conditions being treated as the study of Raebel et al. [53].

Failure to start the first dose of prescribed medications was investigated in clinical trials. Blaschke et al. found that of 16,907 patients in 95 clinical studies, approximately 4% of cases failed to start taking the first dose [54].

1.2.1.2. Suboptimal implementation

Adherence linked with implementation of a dosing regimen represents the level of agreement between a patient’s actual dosing regimen and the prescribed dosing regimen between initiation and discontinuation. Urquhart (1998) proposed a set of patterns of adherence called “rule of sixes” [55]. This rule describes patterns of adherence where approximately one in six patients:

(suboptimal implementation applies from 2 to 6)
1. takes all doses exactly as prescribed
2. takes all prescribed doses but timing is fairly inconsistent
3. misses one occasional dose on any days
4. has a drug holiday three to four times per year
5. has a drug holiday or more than one per month
6. takes few doses or none but creates the impression of good adherence
Based on the dosing history of 4,783 patients with hypertension, Vrijens et al. [56] updated Urquhart’s proposal. The finding of Vrijens et al. is shown in Table 1.6.

Table 1.6: The incidence of various suboptimal adherence patterns. Data are from Vrijens et al. [56].

<table>
<thead>
<tr>
<th>Suboptimal adherence pattern</th>
<th>The proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed one occasional dose at least one time per year</td>
<td>Almost 95%</td>
</tr>
<tr>
<td>Missed an occasional days dose once a month</td>
<td>50%</td>
</tr>
<tr>
<td>Had a drug holiday at least once a year</td>
<td>48%</td>
</tr>
<tr>
<td>Had a drug holiday once per two months</td>
<td>13%</td>
</tr>
</tbody>
</table>

Table 1.6 presents the proportion of patients exhibited different patterns of suboptimal adherence. When considering a particular day, the results showed that 10% of patients who remained persistent with medications did not take their doses. The following results differentiated the types of missed doses on each day, which were summed up as 100%: an omission of an occasional days dose of 42%; one or two sequential days doses of 15%; or a drug holiday of 43% [56].

Although, more specific, these findings do not exclude the rule of sixes of Urquhart, but rather provide an updated understanding of the rates of non-adherence patterns. Given the likelihood of drug holidays, the concern about abrupt discontinuation of taking some medications which may cause rebound effects has been highlighted [54, 55, 57, 58]. It has also been suggested that reinstitution of some medications after periods of missed doses may result in a rejuvenation of the first-dose effect [54, 55, 57, 58]. The first dose-effect is where smaller doses are required for initial doses to prevent adverse drug effects, such as those seen with anti-arrhythmic drugs or α1-adrenergic receptor blockers. Given that patients may exhibit multiple episodes of discontinuation and initiation, these effects may occur more frequently than recognised [54].
1.2.1.3. Early discontinuation

Mechanisms ascribed to early discontinuation include patients prematurely stopping their medications for the current prescription, a failure to refill their subsequent prescriptions, or a failure to re-attend a clinic to reassess a treatment plan. Vrijens et al. proposed that within one year almost 50% of patients with hypertension stopped taking their medications [56]. Blaschke et al. also suggested that approximately 35% of the patients in 95 clinical trials discontinued their medications over one year [54]. It has been noted that 20% of the patients exhibited discontinuation during the first 100 days [54]. However, the finding of Glader et al., which investigated the persistence of secondary preventive medications used in patients with stroke based on prescription refills, showed that 22% of the patients no longer refilled their hypertensive medications (from 96% to 74%) after 2 years [59]. A reduction in the proportion of patients who remained persistent with their medications has been described to be around 44%, 36% and 33% for warfarin, statins and antiplatelet medications, respectively [59]. With regards to antipsychotic medications, Vanelli et al. reported that after 8 months, 52% of patients prescribed with conventional antipsychotics failed to continue to refill their prescriptions with 56% seen in patients prescribed with atypical antipsychotics [60]. Reasons for early discontinuation for antipsychotics were not investigated in the original study. Possible reasons may be due to patients’ beliefs about their illness and the benefits of treatment, and current and past experience of adverse drug effects [61].

1.2.2. Measurement of adherence

Adherence can be measured by many approaches. These can be broadly divided into direct and indirect approaches. Each approach has advantages and disadvantages [8, 62]. Direct approaches include drug concentration measurement in plasma or urine, measurement of a biological marker as well as directly observed therapy. Indirect approaches include patient self-reporting (self-reports based on questionnaires and diaries), returned pill counts,
prescription refill records, clinical response assessment by clinicians and electronic monitoring [8, 47, 62, 63].

Directly observed therapy is when patients are directly observed by healthcare providers at each dose. This method has been used in tuberculosis and HIV [64, 65]. Directly observed therapy is viewed as the most accurate method [8]. However, it seems impractical in routine clinical settings and patients may discard and not actually swallow the pill afterwards [8, 62].

Measuring plasma/urine drug concentrations and biological markers is objective and may reflect the actual therapeutic outcomes of the executed dosing regimen. However, this method is considered expensive [8]. In addition, for a drug that has a short half-life, drug plasma concentration measurement may be affected by “white-coat adherence” [66-68] where patients may create the impression of good adherence by becoming more adherent prior to a clinic visit and returning to their normal behaviour after the clinic visit [8, 62]. It should also be noted that although patients are perfectly adherent, their plasma drug concentrations may not achieve a treatment target due to their pharmacokinetic characteristics e.g. metabolism and excretion. This is the circumstance that the treatment plan is to be revised e.g. dose adjustment but may be confused with poor adherence.

A self-report based on questionnaires appears to be a preferred method in clinical settings given its simplicity and low cost. Limitations for this method include, patients may report overestimated adherence; and they may not recall accurately taken doses and missed doses. The validity of self-reporting depends on some factors including questionnaire item contents, response task, psychometric properties and duration to recall adherence behaviour. For example, the optimal recall duration was variably suggested in different research to be shorter e.g. 4 days or 1 week [69, 70] or longer as 1 month [71]. There was evidence suggesting that adherence measured by self-reports was overestimated using electronic monitoring (will be discussed later in this section) as a comparator [72-75]. However, some studies found that this self-report method was reliable and provided corresponding results of therapeutic
outcomes or of electronic monitoring [76-78]. With regards to a diary, although it is simple to use, patients may modify the content easily. The use of diaries was found biased in [79-81] with a positive finding in [82].

A returned pill count is also easy to perform in clinical settings and inexpensive. Adherence results, however, may not be accurate. “Pill dumping” i.e. patients discard remaining pills could occur prior to clinic visits. In addition, pill counts can only provide global adherence results which is the total number of doses taken. Adherence patterns regarding random missed doses and drug holidays including timing variability, which are important elements in relation to therapeutic attainment, cannot be obtained. The importance of these adherence patterns is discussed in Chapter 3 and Chapter 4. Previous studies suggested that pill count results seemed to overestimate adherence compared to electronic monitoring [72, 79, 83, 84].

Prescription refill records provide results whether patients are adherent at the level of ‘picking up prescribed medications’. However, adherence with respect to initiation, implementation and discontinuation cannot be obtained. That is, patients may pick up prescribed medications but fail to initiate.

The approach of electronic monitoring, whose advantages appear superior to disadvantages, was used in studies in this thesis and will be specifically discussed.

The advent of electronic monitoring devices was noted in the mid 1970s with an eye drop formulation [54, 58]. This eye drop was invented shortly before the micro-electronic era started. Hence, its size and weight were relatively greater compared to traditional eye drops [58]. Due to the unusually large size, which could be described as a large rectangular squeeze bottle [85], it was thought that the data obtained were artefactual [58]. This led to a pause in development between 1977 to 1984 [58]. In 1984, with more advanced technology, a smaller and lighter eye drop electronic monitoring [85] was invented [58]. This eye drop was designed to resemble a traditional 30 mL eye drop container. It was set that only one event could be recorded within a specified interval, 15 minutes. The capacity of data accumulation was around 6
weeks; and data were recorded for approximately 1 year. For analysis, data were transferred by tape to a computer [85]. More recently, several types of electronic monitoring devices have been developed including ones for tablets or capsules [86], inhalers [87, 88], needles disposal [89], medications with blister packaging [90, 91] and poly-medications with blister packaging [92].

A commonly used device in research is the Medication Event Monitoring System (MEMSTM, MWV Switzerland Ltd., Sion, Switzerland). A MEMS looks like a regular tablet or capsule bottle. Its advantage is that it consists of a cap with an installed microprocessor that can record the exact times and dates of the openings of the bottle. The recorded MEMS data are then transferred via a MEMS reader to a computer, which has a MEMS software installed, for analysis [86] (see Figure 1.1). The MEMS data include a profile of when a patient actually takes each dose over time. In general, X-axis is calendar date and Y-axis is 24 hour clock time. The time of the taken dose is represented by the position of a dot along the Y-axis and a missed dose is represented by a vertical bar with clustering vertical bars for consecutive missed doses.

**Figure 1.1:** A Medication Event Monitoring System device connected to its reader to transfer adherence data to a computer

The implicit assumption inherent in studies based on MEMS is that non-adherence is unintentional rather than intentional and that the correct specified number of doses is removed and taken per each opening of the MEMS device. Therefore, patients are usually instructed on how to use the MEMS device e.g. only open the bottle when taking a dose, not to do a “pocket dosing” [93-95],
known as taking more than one pills at a time to take at later time. In some studies, patients were provided with a form along with MEMS to record accident openings of the bottle [73, 96-98]. These events could then be subtracted from the total number of the openings. It was suggested that routine false impression created by non-adherent patients, who opened MEMS at approximately the same time over time but did not take pills, was unlikely given that it required much effort to do so [78]. It was also proposed that to allow a patient’s drug taking behaviour to return to normal behaviour, around the first 5 weeks of MEMS records should be discarded [99, 100]. Wagner and Ghosh-Dastidar reported no significant changes in adherence at the end of 4 weeks compared to baseline [101] whereas Waeber et al. found that adherence significantly decreased after 6 months [102]. Possible explanation that initially patients may be better adherent could be due to “Hawthorne effect” where patient behaviour may improve since they are aware that they are being monitored [96, 98, 103]; or due to the novelty effect where patients may demonstrate how to use MEMS to friends [99]. Although, there is no ‘gold standard’ for measurement of adherence, several studies have considered MEMS as a ‘benchmark’ when comparing the reliability of other indirect approaches e.g. patient self-reporting, pill counts (as discussed earlier). In addition, the benefits of MEMS history data in relation to pharmacokinetics-pharmacodynamics (see section 1.3) leading to success or failure of treatment have been demonstrated [104-109].

1.2.3. Deviation from perfect adherence

The use of MEMS has enabled a quantitative understanding of the three processes of adherence including delayed initiation, early discontinuation and particularly those around implementation. Continuous adherence data in terms of timing data and patterns of adherence have provided a deeper insight into the temporal patterns of how patients take their medications [3, 8, 54, 110]. Large variability in the deviation from perfect adherence has been observed in patients [111] which was not obvious when using the global measure as the number of
doses taken [110]. The importance of using appropriate adherence measures e.g. not using the number of doses taken is discussed in Chapter 3 and Chapter 4.

Markov models have been found to have useful properties for predicting adherence patterns. More broadly, Markov models are used to predict the probability of an event happening/or not happening in a future stage based on current and previous stages. For example, the probability of raining tomorrow may be predicted based on a knowledge of today’s and yesterday’s weather. In an adherence filed, these models are limited to consideration of missed doses and do not incorporate timing variability. In these models, a probability transition matrix is formed that predicts the probability of the next dose being taken or missed depending on the current and previous doses [112]. Equation 1.1 describes the Markov model [111]. Suppose $y_i$ is an event of whether the patient takes the dose or misses the dose at the $i$th time, $p(y_i|y_{i-1})$ is the probability of the current dose being missed or taken based on the previous dose. Missed doses is denoted as 0 and taken doses as 1. Therefore, there are four probabilities that can occur, namely $P_{00}, P_{11}, P_{01}$ and $P_{10}$.

\[
p(y_i = \text{missed dose}|y_{i-1} = \text{missed dose}) = P_{00}
\]
\[
p(y_i = \text{taken dose}|y_{i-1} = \text{taken dose}) = P_{11}
\]
Hence, 
\[
p(y_i = \text{taken dose}|y_{i-1} = \text{missed dose}) = P_{01} = 1 - P_{00}
\]
\[
p(y_i = \text{missed dose}|y_{i-1} = \text{taken dose}) = P_{10} = 1 - P_{11}
\]

**Equation 1.1:** Probability of a taken dose or a missed dose based on the previous dose

The Markov probability transition matrix ($P_{\text{Markov}}$) is then constructed of the four probabilities as per Equation 1.2 [111]. In the Markov case the transition probabilities are estimated.

\[
P_{\text{Markov}} = \begin{bmatrix} P_{00} & P_{01} \\ P_{10} & P_{11} \end{bmatrix}
\]

**Equation 1.2:** The Markov probability transition matrix
In Chapter 5, Poisson distribution and an empirical distribution were used to simulate random missed doses and drug holidays, respectively. Markov models were not used in this thesis since the goal was to simulate acceptable patterns of non-adherence rather than to learn about how patterns of non-adherence arise.

To provide an empirical description of how patients may exhibit a variety of adherence patterns, once daily dosing anticoagulant adherence profiles with a monitoring period of 90 days (n=23) have been reviewed from an online resource, www.iAdherence.org. The following data were summarised: (1) number of patients exhibiting random missed doses over 90 days (Figure 1.2); (2) number of patients exhibiting two consecutive missed doses over 90 days (Figure 1.3); and (3) number of patients exhibiting drug holidays over 90 days (Figure 1.4).

Overall, the results show that (1) 4, 3, and 2 patients had 1 or 3, 0, and 2 or 5 random missed doses over 90 days, respectively; (2) 17 and 4 patients had 0 and 1 two consecutive missed doses over 90 days, respectively; and (3) 20 patients had none of drug holidays.

![Figure 1.2: Number of patients exhibiting random missed doses over 90 days](image)
1.3. Association between adherence and the time course of drug effects

1.3.1. Pharmacokinetics

Pharmacokinetics (PK) describes the relationship between drug concentration and time. PK involves studying drug absorption, distribution and elimination, i.e. metabolism and excretion. More broadly, the PK process can be described as two phases: 1) input and 2) disposition. The input phase, for an orally administered drug, comprises the processes of drug disintegration, dissolution and absorption after administration. The disposition phase includes distribution and elimination (renal or hepatic). These two processes of input and disposition occur simultaneously.
Chapter 1: Introduction

Therapeutically, attaining the right concentration at the site of action is the goal where the concentration is optimised to produce the best pharmacological response with minimal toxicity. In some circumstances a therapeutic range has been described in which the benefits outweigh the risks. However, it is not always practical and possible to measure the drug concentration at the site of action. Hence, the plasma concentration is usually measured as a surrogate of the drug concentration at the site of action.

To describe the PK process, the body is viewed as a series of compartments where a compartment is a theoretical representation of a set of tissues with similar rates of drug distribution that are lumped together. The simplest scenario identifies the whole body as a single compartment (Figure 1.5). This single compartment represents all body tissues and includes the plasma. The drug distributes instantaneously and uniformly throughout the compartment. The classic example that can be described by this one-compartment PK model is intravenous (IV) bolus administration where there is no evidence of a distinct time course of distribution and first-order elimination dominates the plasma concentration resulting in a monoexponential decline in concentrations (Equation 1.3, which is derived from Figure 1.5, and Figure 1.6).

![Figure 1.5: Schematic of a one-compartment PK model for IV bolus administration with first-order elimination. V = apparent volume of distribution in the central compartment. k = elimination rate constant.](image-url)
\[
\frac{dA}{dt} = -k \times A; \quad A_0 = D
\]

\[A(t) = D \exp(-k \times t); \quad k = \frac{CL}{V} \]

\[C(t) = \frac{D}{V} \exp \left( -\frac{CL}{V} \times t \right) \]

**Equation 1.3:** One-compartment PK model for IV bolus administration with first-order elimination described as a mass balance equation where \(\frac{dA}{dt}\) is the rate of change of drug. \(A\) = amount in the central compartment, \(k = \frac{CL}{V}\) = elimination rate constant, \(CL\) = clearance, \(V\) = apparent volume of distribution, \(A_0\) = initial condition of \(A\), \(D\) = dose. After integration, \(A(t)\) = amount at time \(t\).

After converting the amount to concentration, \(C(t)\) = plasma concentration at time \(t\).

**Figure 1.6:** Concentration vs time profile for a one-compartment PK model for IV bolus administration with first-order elimination; \(D = 1\) mg, \(CL = \ln(2)\) L/h, \(V = 1\) L.

A one-compartment PK model for oral administration is described by the schematic in Figure 1.7. Corresponding mass balance equations with integrated forms are given by Equation 1.4.
Figure 1.7: Schematic of a one-compartment PK model for oral administration with first-order absorption and elimination depicted as the gut compartment and the body (central) compartment. $F =$ oral bioavailability, $k_a =$ absorption rate constant. $V =$ apparent volume of distribution in the central compartment. $k =$ elimination rate constant.

\[
\begin{align*}
\frac{dA(1)}{dt} &= -k_a \times A(1); A_0(1) = D \\
\frac{dA(2)}{dt} &= k_a \times A(1) - k \times A(2); A_0(2) = 0 \\
A(t) &= \frac{D \times F \times k_a}{k_a - k} \left[ \exp(-k \times t) - \exp(-k_a \times t) \right] \\
C(t) &= \frac{D \times F \times k_a}{V \left( k_a - \frac{CL}{V} \right)} \left[ \exp\left(-\frac{CL}{V} \times t\right) - \exp(-k_a \times t) \right]
\end{align*}
\]

Equation 1.4: One-compartment PK model for oral administration with first-order absorption and elimination. $A(1) =$ amount in the gut, $A_0(1) =$ initial condition of $A(1)$, $A(2) =$ amount in the central compartment, $A_0(2) =$ initial condition of $A(2)$. After integration, $A(t) =$ amount at time $t$. After converting the amount to concentration, $C(t) =$ plasma concentration at time $t$. 
1.3.2. Pharmacodynamics

Pharmacodynamics (PD) describes the relationship between drug concentration at the site of action and drug effect. Here, the drug at the site of action binds a receptor to generate a biochemical and subsequent physiological effect. When competitive binding predominates, the relationship between concentration and effect can be described as a hyperbolic function. At lower concentrations, increased concentration results in proportionally increased effect. At higher concentrations, the relationship behaves according to a law of diminishing returns. Eventually, the effect asymptotes to a maximum effect irrespective of increased concentration.

In general, the binding of a drug to a receptor (e.g. ion channels or enzymes) to form an activated drug-receptor complex is governed by the principles of mass action (Equation 1.5). The interaction between the drug and the receptor results in initial stimulus. The initial stimulus is then relayed to the inside of cells. This transduction process usually involves a series of reactions leading to observed drug effect.

\[
D + R \stackrel{k_{on}}{\rightleftharpoons} DR
\]

*Equation 1.5: Binding of a drug to a receptor*

where \(D\) is a drug, \(R\) is a receptor, \(DR\) is an activated drug receptor complex, \(k_{on}\) is the association rate constant of a drug with a receptor, \(k_{off}\) is the dissociation rate constant of a drug with a receptor.

Therefore, at equilibrium, constant \((k_d)\) is given by;

\[
k_d = \frac{k_{off}}{k_{on}}
\]

*Equation 1.6: Dissociation constant at equilibrium*

\(k_d\) denotes the inverse of the affinity of the receptor for the drug at equilibrium.
After computing fractional receptor occupancy, which is similar to the Michaelis-Menten equation, receptor binding can then be expressed as Equation 1.7.

\[ B = \frac{B_{\text{max}} \times C}{k_d + C} \]

**Equation 1.7: Receptor binding equation, the \( B_{\text{max}} \) model**

where \( B \) is the concentration of bound receptors, \( C \) is the drug concentration, \( B_{\text{max}} \) is maximum binding equivalent to the maximum number of receptors.

For practicality in clinical settings where the receptor binding information is not available, the \( B_{\text{max}} \) model is expressed as an \( E_{\text{max}} \) model (Equation 1.8) using the link of the proportionality constant, under the assumption that the clinical effect is proportional to \( B \) [113].

\[ E = \frac{E_{\text{max}} \times C}{EC_{50} + C} \]

**Equation 1.8: The \( E_{\text{max}} \) model**

where \( E_{\text{max}} \) is the maximum effect of the drug, \( C \) is the drug concentration, \( EC_{50} \) is the drug concentration resulting in half maximal effect.

To account for multiple binding sites at the same receptor, an addition to the \( E_{\text{max}} \) gives a sigmoidal \( E_{\text{max}} \) model (Equation 1.9) where the parameter \( \gamma \) called the Hill coefficient affects the slope of the effect-concentration relationship to be steeper (values of \( \gamma \) greater than one) or shallower (values of \( \gamma \) lower than one), see Figure 1.8. The Hill equation was originally developed to describe the binding of oxygen to haemoglobin [114].

\[ E = \frac{E_{\text{max}} \times C^\gamma}{EC_{50}^\gamma + C^\gamma} \]

**Equation 1.9: The sigmoidal \( E_{\text{max}} \) model**
Figure 1.8: Concentration-effect relationship for an $E_{\text{max}}$ model with $E_{\text{max}} = 1$ and $EC_{50} = 1.3$ mg/L where blue line, $\gamma = 1$; red line, $\gamma = 0.25$ and green line, $\gamma = 5$.

To account for baseline physiological conditions (e.g. blood glucose, blood pressure baseline), a modification to the $E_{\text{max}}$ model can be made where $E_0$ is included (Equation 1.10).

$$E = E_0 + \frac{E_{\text{max}} \times C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

**Equation 1.10:** The $E_{\text{max}}$ model with the baseline of the system ($E_0$)

1.3.3. Pharmacokinetics-Pharmacodynamics

Combining PK and PD, Pharmacokinetics-pharmacodynamics (PKPD), provides a description of the time course of drug effect. Figure 1.9 illustrates the combination of PK i.e. the time course of drug concentration (Figure 1.9 a) and PD i.e. the relationship between concentration and effect (Figure 1.9 b) to generate a PKPD profile i.e. the time course of drug effect (Figure 1.9 c).
Figure 1.9: Illustration of a PKPD model by combining (a) PK, a concentration-time profile and (b) PD, an effect-concentration profile to obtain (c) PKPD, an effect-time profile.

PKPD models can be mainly categorised into:

- Immediate effects PKPD models
- Delayed effects PKPD models

1.3.3.1. Immediate effects PKPD models

An immediate effects PKPD model depicts the plasma concentration of drug as the direct driver of effect. Therefore, the maximum effect is attained at the same time as the maximum plasma drug concentration (Figure 1.10). An example of an immediate effects PKPD model is given by Equation 1.11 where the plasma concentration at any time, \( C(t) \) is substituted in the \( E_{\text{max}} \) model as per Equation 1.8.

\[
E(t) = \frac{E_{\text{max}} \times C(t)}{EC_{50} + C(t)}
\]

Equation 1.11: Immediate effects PKPD models

In general, it is assumed that patients are perfectly adherent. That is, each dose is taken at each dosing interval.
1.3.3.2. Delayed effects PKPD models

A delayed effects PKPD model allows the time course of effect to be delayed in relation to the time course of plasma drug concentration. The delay effects phenomenon can occur due to 1) a delay in distribution of the drug from plasma to the effect site and 2) the time course of the turnover process of biological substance. Therefore, there are two types of delayed effects PKPD models as follows:

- Effect compartment PKPD models
- Turnover PKPD models

The effect compartment PKPD model [115] considers the situation that the effect site is distal to the intravascular compartment. A hypothetical effect compartment allows for the time required for the drug to equilibrate between the plasma and effect site, which results in the delay in distribution. Note that the effect related to the effect site drug concentration is immediate. Therefore, it can be conceptualised that the effect compartment is a link between the PK model and the PD model i.e. the effect compartment concentration is a driver from the PK model to the PD model. It is assumed that the amount of drug

**Figure 1.10:** Concentration vs time (blue line) and effect vs time (green line) profiles for an immediate effects PKPD model with $E_{\text{max}} = 1$, $EC_{50} = 1.3$ mg/L. The PK model used is a one-compartment model for oral administration with first order-absorption and elimination where $D = 100$ mg, $CL = 20$ L/h, $V = 4$ L and $k_a = 1/h$. 


distributing to the effect compartment is small and hence has negligible impact on mass-balance. Although the volume of the effect compartment cannot be determined, the rate constant of loss from the effect compartment can be estimated and the equilibrium rate constant \( k_{eq} \) is estimated. The link effect compartment model and the effect compartment PKPD model are given by Equation 1.12 where \( C_e(t) \) is substituted in the \( E_{max} \) model as per Equation 1.8.

\[
\frac{dC_e}{dt} = k_{eq} \times (C(t) - C_e)
\]

\[
E(t) = \frac{E_{max} \times C_e(t)}{EC_{50} + C_e(t)}
\]

**Equation 1.12:** The link effect compartment model and the effect compartment PKPD model. \( C_e \) is the effect compartment concentration, \( k_{eq} \) is the equilibrium rate constant.

The turnover PKPD model [116, 117] describes a drug effect which involves in stimulation (or inhibition) of production (or elimination) of a physiological intermediate. The time course of these physiological processes i.e. the turnover of physiological intermediates, which is the rate limiting step results in the delayed effect. Table 1.7 presents four turnover PKPD models based on each mechanism of the drug acting on physiological intermediates.

**Table 1.7:** Four turnover models based on each mechanism of the drug acting on physiological intermediates (I). \( R_{in} \) = zero-order production rate of I, \( I_{max} \) = maximum degree of inhibition (0<\( I_{max} \)<1), \( S_{max} \) = maximum degree of stimulation, \( k_{out} \) = elimination rate constant.

<table>
<thead>
<tr>
<th>Mechanism of the drug acting on physiological intermediates leading to decreased or increased effect</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inhibition of production</td>
<td>Decreased effect</td>
</tr>
<tr>
<td>[ \frac{dI}{dt} = R_{in} \times \left( 1 - \frac{I_{max} \times C(t)}{EC_{50} + C(t)} \right) - k_{out} \times I ]</td>
<td></td>
</tr>
<tr>
<td>2. Inhibition of elimination</td>
<td>Increased effect</td>
</tr>
<tr>
<td>[ \frac{dI}{dt} = R_{in} - k_{out} \times \left( 1 - \frac{I_{max} \times C(t)}{EC_{50} + C(t)} \right) \times I ]</td>
<td></td>
</tr>
<tr>
<td>3. Stimulation of production</td>
<td>Increased effect</td>
</tr>
<tr>
<td>[ \frac{dI}{dt} = R_{in} \times \left( 1 + \frac{S_{max} \times C(t)}{EC_{50} + C(t)} \right) - k_{out} \times I ]</td>
<td></td>
</tr>
<tr>
<td>4. Stimulation of elimination</td>
<td>Decreased effect</td>
</tr>
<tr>
<td>[ \frac{dI}{dt} = R_{in} - k_{out} \times \left( 1 + \frac{S_{max} \times C(t)}{EC_{50} + C(t)} \right) \times I ]</td>
<td></td>
</tr>
</tbody>
</table>
The turnover model 1 is used in Chapter 6 for atorvastatin for the inhibition of LDL production.

1.3.4. Heterogeneity and uncertainty

When applying PKPD models to describe a patient’s drug response, it is crucial to consider heterogeneity between patients, often termed between subject variability (BSV). BSV comprises predictable and unpredictable variability. Predictable variability can arise from patient characteristics i.e. covariates such as age, sex, weight, height, body composition and organ function e.g. renal function. Information obtained from these covariates explains some of the variability observed among patients in the population. That is, it explains when an individual patient’s drug response differs from an average (or typical) patient’s drug response where an average patient is a patient with mean population parameter estimates.

Uncertainty about the observations is provided by the remaining variability, often termed residual unexplained variability (RUV). RUV can arise from four sources, namely (1) process error, (2) measurement error, (3) model misspecification and (4) moment to moment variability [118].

Considering BSV for parameter CL in Equation 1.3 \( C(t) = \frac{D}{V} \exp \left( -\frac{CL}{V} \times t \right) \), we now have \( CL \) population average = \( \overline{CL} \). Therefore, \( CL \) for the \( i \)th individual (\( CL_i \)) is given by Equation 1.13.

\[
CL_i = \overline{CL} \exp(\eta_i) ; \eta_i \sim N(0, \omega^2)
\]

**Equation 1.13:** The \( i \)th individual’s parameter value accounting for BSV

where \( \eta_i \) is the difference of an individual from the population average for the \( i \)th individual which is assumed to be log-normally distributed resulting in positive values of \( CL_i \) and with a mean 0 and variance \( \omega^2 \).

When considering RUV, \( \varepsilon_{ij} \) is the difference of an observation from a model prediction for the \( i \)th individual at the \( j \)th observation. It is assumed to be an independent identically distribution normal deviate with a mean 0 and variance \( \sigma^2 \). Hence Equation 1.3 becomes:
\[ C_{ij} = \frac{D_i}{V_i} \exp \left( - \frac{C L_i}{V_i} \times t_{ij} \right) + \epsilon_{ij}; \; \epsilon_{ij} \sim N(0, \sigma^2) \]

**Equation 1.14:** Concentration for the ith individual at the jth time point \( t_{ij} \) (\( C_{ij} \)) accounting for RUV

This concept of heterogeneity and uncertainty was applied in a model-based meta-analysis work in Chapter 2. In Chapter 5 and Appendix A.3.3, BSV and RUV were incorporated in population PKPD models. BSV was also considered in Chapter 6.

### 1.3.5 Illustration of the impact of imperfect adherence on the time course of drug effects

First, an indicative example of an adherence profile recorded by MEMS is shown in Figure 1.11. This is a once daily dosing profile. X-axis is calendar date. Y-axis is 24 hour clock time. Each blue dot depicts the exact timing that the patient opens a MEMS bottle to take a dose. Each vertical bar depicts a single missed dose.

![Figure 1.11](image)

**Figure 1.11:** An indicative example of a MEMS profile. X-axis is calendar date (day/month/year). Y axis is 24 hour clock time (from 3:00 am to 2:59 am). Each blue dot represents the exact timing that the patient opens a MEMS bottle. A vertical bar represents a missed dose.

Figure 1.12 illustrates an average patient with mean population parameter estimates in two scenarios, (1) perfect adherence (left panel) and (2) imperfect adherence (right panel). A one-compartment instantaneous unit input PK model linked to an immediate effects \( E_{\text{max}} \) PD model is used as an illustrative example. Parameter values are provided in Table 1.8. The first row depicts a MEMS profile where the patient takes drugs at the nominal time every day for perfect adherence.
adherence; and an imperfect adherence profile consists of timing variability, random missed doses and drug holidays. The second row and the third row show the impact of drug taking behaviour on a PK profile and a PKPD profile, respectively. The red line indicates a hypothetical target threshold for success. It can be seen that for perfect adherence, the PKPD profile is always above this threshold. In contrast, for imperfect adherence, timing variability results in the fluctuating PK and PKPD profiles. A random missed dose results in the effect being below the threshold (green circles). It is more pronounced when drug holidays occur (red circles).

Details, worked examples and quantification of these profiles are discussed in Chapter 5.

**Figure 1.12:** Comparison of an average patient with perfect adherence (left panel) and imperfect adherence (right panel). The model used is a one-compartment instantaneous unit input PK model linked to an immediate effects $E_{\text{max}}$ PD model. The top row is a MEMS profile. The middle row is a PK profile. The bottom row is a PKPD profile. The red line indicates a hypothetical target threshold for success. The green circles indicate the relationship between a random missed dose and a decrease in concentrations and effects. The red circles indicate the relationship between a drug holiday and a decrease in concentrations and effects.
Table 1.8: Parameter values for the illustration of the impact of imperfect adherence on the time course of drug effects

<table>
<thead>
<tr>
<th>Parameter/variable*</th>
<th>Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>1</td>
</tr>
<tr>
<td>CL (L/d)</td>
<td>ln(2)</td>
</tr>
<tr>
<td>V (L)</td>
<td>1</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>1</td>
</tr>
<tr>
<td>$EC_{50}$ (mg/L)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

* CL is clearance. V is apparent volume of distribution. $E_{\text{max}}$ is maximum effect. $EC_{50}$ is drug concentration resulting in half maximal effect.

* Note the units are arbitrary and provided for interpretation of once daily dosing profiles.

1.3.6. Choice of drugs as an alternative to assist patients with suboptimal adherence

1.3.6.1. Drugs and dosing regimens that are associated with greater adherence

1.3.6.1.1. Reducing the frequency of drug administration

It has been proposed that lower frequency of daily dosing regimen, e.g. once daily compared to thrice daily dosing, results in higher adherence across a variety of diseases [119, 120]. The findings of the systematic review of Claxton et al. [119] are presented in Table 1.9. It should be noted that the findings were derived from the mean percentage of prescribed doses taken data and hence adherence patterns were not taken into account.

Table 1.9: Mean percentage of prescribed doses taken recorded by MEMS based on different frequency of dosing regimens. Data are from Claxton et al. [119].

<table>
<thead>
<tr>
<th>Frequency of dosing regimen</th>
<th>Mean percentage of prescribed doses taken recorded by MEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily</td>
<td>79%±14%</td>
</tr>
<tr>
<td>Twice daily</td>
<td>69%±15%</td>
</tr>
<tr>
<td>Thrice daily</td>
<td>65%±16%</td>
</tr>
<tr>
<td>Four times daily</td>
<td>51%±20%</td>
</tr>
</tbody>
</table>
Several drugs have been developed as extended release formulations including depots, implants, transdermal patches and oral formulations. Since various methods were used to monitor adherence in the literature, the following studies may relate to the global measure of adherence and not to adherence patterns. Where possible, adherence pattern related findings are presented. A systematic review and meta-analysis of Leucht et al. investigating adherence of depot compared to oral drugs in patients with schizophrenia showed a significant advantage of depot formulations in decreasing the rate of relapse (relative risk (RR)=0.70, confidence interval (CI)=0.57-0.87, p=0.0009) [121]. The antipsychotic depot formulations reviewed in this study [121] included fluphenazine decanoate, zuclopenthixol, haloperidol and risperidone. Similarly, with regards to contraception, it has been shown that adherence was significantly higher in participants who used a contraceptive transdermal patch (Ortho Evra®, norelgestromin and ethinyl estradiol), which was applied weekly, at 88.2% compared to those who took an oral contraceptive daily at 77.7% (p<0.001) [122]. It has also been reported that the use of contraceptive implants (Norplant®, levonorgestrel) compared to oral contraceptives in adolescents was associated with significantly higher adherence based on a decision of continuing using implants at follow-up. The rate of new pregnancies were also significantly lower in the implant group compared to the oral contraceptive group (38% vs 2%, p<0.001; the number of enrolled participants were 50 and 48 in oral contraceptive and implant groups, respectively) [123]. In addition, the study of Kardas comparing adherence between once daily slow-release isosorbide mononitrate and twice daily isosorbide dinitrate for stable angina pectoris reported that the percentage of days with correct number of doses taken monitored by MEMS was significantly higher in the slow-release isosorbide mononitrate compared to the isosorbide dinitrate groups (85.5% vs 59.5%, p<0.0001, respectively) [124].

An alternative strategy to the choice of extended release formulations is the choice of drugs that have a long half-life as an inherent property. In a hypertension study by Andrejak et al. using MEMS to monitor adherence
showed that patients prescribed with trandolapril (half-life around 6 hours) given once daily were significantly more adherent than those prescribed captopril (half-life less than 3 hours) and used twice daily (98.9% vs 97.5%, p=0.002) [125]. A corresponding finding was shown in a stable angina pectoris when comparing betaxolol once daily vs metropolol twice daily with a measured adherence of 86.5% and 76.1% (p<0.01) [126].

However, the systematic review of Claxton et al. only found the statistical benefits between the reduction of four times to once daily; four times to twice daily; and thrice to once daily dosing regimens [119].

1.3.6.1.2. Reducing number of medications

Fixed-dose combination medications (aka the polypill) have been formulated for several therapeutic areas including HIV, hypertension and diabetes. The choice of fixed-dose combinations reduces pill burden. Maitland et al. investigated adherence in patients with HIV prescribed with once daily fixed-dose combination of abacavir and lamivudine compared to twice daily abacavir and lamivudine [95]. The results suggested the significantly higher adherence rates in those prescribed with once daily fixed-dose combination compared to those prescribed with twice daily dosing. The percentage of doses taken on schedule measured by MEMS was 95.5% (53.8–100%) vs 86.3% (4.3–100%), p=0.006, respectively [95]. This study combines the influence of reduced pill burden with dosing regimen simplification and demonstrates the benefits of this combined approach.

1.3.6.2. Drugs that are forgiving: introduction to forgiveness

The concept of forgiveness was introduced by Urquhart in 1997 [57]. Forgiveness can be generally viewed as how accommodating a drug is to less than perfect adherence. The forgiveness property of drugs arises from the relationship of the duration of action and the dose interval of the drug. When the duration of action greatly exceeds the dose interval then the drug is considered forgiving to timing errors or missed doses. In this setting it is expected that one or two missed dose(s) might have minimal effects on the therapeutic benefits.
Forgiveness arises from two main processes: (1) drugs with a long half-life in relation to their dosing interval which leads to persistent plasma concentrations and (2) drugs that cause an effect that is persistent after the plasma drug concentrations have been essentially washed out. Therefore, the choice of forgiving drugs may accommodate patients with suboptimal implementation.

Forgiveness (F) of each drug can be described as the duration of effect (D) minus dosing interval (I) (as per [57]), shown as: \( F = D - I \). Based on this concept it is possible to evaluate the forgiveness of a drug that has a duration of drug effect for 72 hours (i.e. D = 72 hours) and is prescribed as a once daily dosing regimen (i.e. I = 24 hours); forgiveness is \( 72 - 24 = 48 \) hours. This can be normalised to the dose interval (i.e. \( 48 \div 24 \)) to yield a forgiveness index of 2. This implies that omission of two consecutive doses would not be expected to have a significant impact on therapeutic outcomes. An example of a drug with a forgiveness index of 2 is amlodipine used for hypertension treatment [127]. In contrast, a classic example of unforgiving drugs is most progestin only pills for contraception (minipills) since they must be taken within three hours of the same time every day.

It has been demonstrated that, to determine the duration of effect of a drug, some clinical studies have replaced the drug with placebo and then measured the remaining duration of effect. This approach has been conducted, when ethically appropriate, in some studies including contraception, hypertension and depression [128]. Duration of effects of each therapeutic area can be measured based on observable biomarkers such as systolic blood pressure reduction; or validated instruments for signs and symptoms [129, 130]. It is also possible to predict the duration of drug effect using principles based on PKPD (see [131, 132] for a description of these processes).

For drugs that are dosed chronically and have a long half-life relative to the dose interval it is anticipated that the drug would be forgiving (Table 1.10). Note that this is a simplification of the true forgiveness as it only accounts for plasma drug half-life and not the effects of the drug which may be prolonged further.
Table 1.10: Drugs used chronically that have a long half-life and are prescribed once daily or more frequent (I ≤ 24 hours) [133].*

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Usual dose interval</th>
<th>Half-life</th>
<th>Forgiveness index</th>
</tr>
</thead>
<tbody>
<tr>
<td>diazepam</td>
<td>6-12 hours</td>
<td>43 hours</td>
<td>2.5-6</td>
</tr>
<tr>
<td>phenobarbitone</td>
<td>8-12 hours</td>
<td>99 hours</td>
<td>7-11</td>
</tr>
<tr>
<td>amiodarone</td>
<td>24 hours</td>
<td>25 days</td>
<td>24</td>
</tr>
</tbody>
</table>

*This list excluded anticancer agents and monoclonal antibodies.

There are few drugs that fulfil this requirement based on plasma drug half-life alone. The plasma drug half-life is, however, only one of several determinants of the duration of therapeutic effect. The duration is also a function of the effects of the drug on the physiological system. These effects may be prolonged by comparison to the plasma drug half-life based on two mechanisms (1) the drug affects a biological intermediate that has a slow turnover and (2) drugs whose response accumulates over time.

The former mechanism is typical for a drug that affects the turnover of an endogenous substance. For instance, the active metabolite of simvastatin, simvastatin acid, inhibits production of cholesterol via inhibition of HMG-CoA reductase. Although the active metabolite has a half-life of 2-3 hours simvastatin is prescribed as a once daily dosing regimen. Importantly, the duration of effect is driven by the half-life of LDL which is in the order of 3-4 days giving a duration of action of approximately 3 days [134]. Here the duration of effect is essentially independent of the plasma drug half-life and considerably longer than the dose interval. With a forgiveness index of approximately 3, this means that simvastatin is a relatively forgiving drug and the occasional missed dose is unlikely to be problematic. This has been supported by simulation studies [132].

Accumulation of drug response over time occurs in settings where the drugs actions are distal to the plasma and where the drug distributes to a site where the turnover of the tissue at the site is slow relative to plasma drug half-life. An example of this is alendronate which for treatment doses is prescribed either 10 mg daily or 70 mg weekly. Both dosing regimens provide therapeutic outcomes of an increase in bone mineral density [135]. The plasma alendronate
half-life is approximately one hour; however it is forgiving since its target site, bone, has a turnover half-life of much greater than 1 year. Hence, accumulation in bone continues over a much longer time frame than in the plasma. Therefore, an occasional missed dose or even a drug holiday will not be expected to result in loss of therapeutic effect.

In some circumstances, several effects that result in forgiveness may be combined. Warfarin is an example of a forgiving drug from two processes. Warfarin has a long half-life of approximately 40 hours (compared to a dosing interval of 24 hours). It inhibits the production of vitamin K dependent clotting factors: II, VII, IX and X each with their own half-life of turnover (factor II has a half-life of approximately 60 hours). This results in the duration of warfarin effect of at least 3 days. Here the duration of effect is dependent on both the plasma warfarin half-life and the turnover of the factors. In contrast, dabigatran has a shorter half-life of 12-17 hours and is a competitive antagonist of factor IIa and hence has no intermediate effects seen with warfarin. Therefore, while a missed occasional dose of warfarin would not affect therapeutic response, a missed occasional dose of dabigatran may run the risk of adverse therapeutic effects.

A formal way to quantify forgiveness is discussed in Chapter 5 with an example of how it can be applied in clinical practice in Chapter 6.
1.4. *Aims of this thesis*

The overarching aim of this thesis is to quantify adherence, the influence of factors on adherence and the influence of adherence on therapeutic outcomes. The specific aims for each chapter are:

1. To determine the independent influence of disease and other factors on adherence.
2. To investigate adherence measures used in MEMS literature and determine appropriate adherence measures.
3. To investigate the feasibility of conducting the first MEMS study in New Zealand and explore adherence patterns given the collected data.
4. To develop a relative forgiveness criterion and quantify the forgiveness of drugs to imperfect adherence.
5. To apply the developed relative forgiveness criterion to adherence profiles observed in clinical practice.

Given that there have been many attempts to improve adherence with inconclusive findings, this thesis explores an alternative approach involving consideration of forgiving drugs. That is, the choice of drugs that may be forgiving to imperfect adherence is under consideration.
Chapter 2: A model-based meta-analysis of the influence of factors that impact on adherence

This chapter is based on the following peer-reviewed publication:

2.1. Context

There have been several studies that have investigated factors that may influence adherence for each disease and the range of diseases covered was fairly broad such as HIV, hypertension, diabetes, asthma, depression and epilepsy [12]. However, since the studies were conducted within a particular disease, the influence of disease on adherence could not be explored.

Less work has been conducted to investigate the influence of disease type and other factors on adherence across different disease types. In addition, current analyses in the literature consider the disease factor in a univariate manner and thus cannot delineate the independent influence of disease type from other factors.

2.2. Aims

The aim of this study is to determine the independent influence of disease and other factors on adherence.

2.3. Methods

This study describes a model-based meta-analysis (MBMA) of studies that have addressed adherence across different diseases and other factors influencing adherence.

MBMA concurrently accounts for many factors of interest. In addition, continuous response measures can be taken into account [136]. That is, analyses are conducted in the manner of multivariate analyses with continuous outcomes. Examples of previous literature using this MBMA technique with time being treated as continuous variables are as follows: [137-140] MBMA also considers both fixed effects and random effects which is of crucial since there may be variability of data being pooled from different studies.
2.3.1. Literature search

A literature search was conducted to retrieve adherence studies using Medication Event Monitoring System (MEMS) devices. A literature search was performed using Medline. Search terms included “compliance” or “patient compliance” or “patient adherence” or “medication adherence” combined with “medication event monitoring system” or “MEMS” or “electronic monitoring”; where appropriate terms were exploded to include all subterms. The years of search included were from 1949 until November 2011.

2.3.2. Study selection

Studies were categorised into different therapeutic areas based on titles and abstracts. Only the two most commonly studied therapeutic areas were selected for inclusion in the analysis. Studies relating to the two most commonly studied therapeutic areas were reviewed based on their full-text. Inclusion criteria for analysis were: 1) The study must use a MEMS device to measure adherence. 2) Minimum study duration was 2 weeks. 3) If it is an intervention study that was designed to improve adherence then the study must have a control arm (which would be used for analysis). 4) There must be an active drug arm. Exclusion criteria for analysis were: 1) Adherence was not reported from MEMS. 2) The focus of MEMS research was not on reporting adherence results according to defined adherence criterion including percentage of prescribed doses taken per day, percentage of days with correct frequency of prescribed doses taken and percentage of prescribed doses taken on schedule. 3) The study reported an intervention (patients being offered adherence education) with no control arms (i.e. the influence of the factors could not be assessed independently of the adherence-based intervention). 4) Research that had the same group of patients studied as research that the authors already included. 5) The study was a review. 6) The study reported methodologies with no results. 7) The report was an editorial comment, editorial letter, correspondence. 8) Results that were reported did not originate from the research undertaken. 9) Only patients with known suboptimal adherence were recruited. 10) Study duration was too short (less
than 2 weeks). 11) The medicines were not a solid dosage form (e.g. liquid medications). Subsequently, the most commonly recorded adherence criterion was used to filter studies.

### 2.3.3. Data extraction

All studies with the most commonly recorded adherence criterion included for data extraction contained the number of patients, disease, age, dosing regimen and mean or median adherence results. Studies were excluded prior to data extraction if they met the following criteria: 1) The study contained missing data that could not be imputed based on our assumptions. (Assumptions are shown in Appendix A.1.1). 2) Adherence results were only reported as the proportion of patients with adherence levels i.e. 80% or 95% adherence. Data imputation, please refer to Appendix A.1.1 for further details, is as follows: 1) Number of patients: If the number of patients that completed the study was not provided then the number of patients was set to the number of enrolled patients; 2) Dosing regimen: If the dosing regimen was not directly reported then it was implied from other content in that study where possible; 3) Age: If the age of an individual group was not provided then the average age of all enrolled patients was used; and 4) Adherence result: If more than one value for adherence was reported (for instance adherence could be reported over different time periods) then the average adherence was used.

Pseudo-patient level data were extracted from each study which included disease, age, dosing regimen, mean or median adherence results. Here the term *pseudo* is used since each patient’s results were seldom reported. Where individual patient level data (actual data of each individual patient) were not provided then patient data from the study were created by single imputation of the mean study attributes. For example, a study of 50 individuals would be created based on 50 individuals having the mean attributes of the study. Where these were described in a multivariate manner, for example the age of males and females were provided separately, then the patient level data were created to reflect this detail. In all cases a study index was added to the data set so that a
study level random effect could be included. Assuming each study provides data on a single individual on only 1 occasion then a patient level random effect is not required. When more than 1 study is reported in the same article a random effect was considered for within publication variability.

The extracted data were analysed using a MBMA technique under a nonlinear mixed effects modelling framework using NONMEM® 7.2 (ICON Solutions, Ellicott City, MD, USA). This technique provided an estimate of the combined (unadjusted) and independent (adjusted) influence of each factor on adherence. Note this does not imply that an independent (adjusted) factor is causally associated.

2.3.4. Model building

An expit transformation was used to transform the predicted adherence percentage to lie between 0% and 100%. Note the addition of a residual error term allows adherence values to exceed 100%.

A general form of the model to predict adherence is given by, \( g_{ij} \):

\[
g_{ij} = \beta_0 + \beta_1 X_{ij} + \eta_i
\]

**Equation 2.1: A general form of the model to predict adherence**

where \( g_{ij} \) is the linear predictor, \( \beta_0 \) is the intercept, \( \beta_1 \) is the factor coefficient, \( X_{ij} \) is the factor for the \( j \)th patient in the \( i \)th study, and \( \eta_i \) is the between study random effect for the \( i \)th study. Note here that further factors and coefficients and interaction terms can be added to determine the adjusted influence of each factor of interest.
Under the expit transformation, the linear predictor is transformed according to

\[ y_{ij} = \left( \frac{1}{1 + e^{-g_{ij}}} \right) 100 + \varepsilon_{ij} \]

Equation 2.2: Transformation of the linear predictor

where \( y_{ij} \) is the observed individual adherence data (as a percentage) for the \( j \)th patient in the \( i \)th study and \( \varepsilon_{ij} \) is residual unexplained variability which is assumed to be an independent and identically distributed (i.i.d.) normal deviate.

The factors of interest were disease, age, dosing regimen, duration of treatment, medication class and pill burden. Disease was treated as a nominal variable and age was treated as a continuous variable centred by the mean value. With regard to dosing regimen, models with ordinal, nominal and continuous dosing regimens were considered. Dosing regimen was summarised as: 1 = once daily dosing, 2 = twice daily dosing, 3 = thrice daily dosing etc. In circumstances when a study may have included either once or twice daily dosing then the dosing regimen was set to the mean (1.5) and so forth. Duration of treatment was defined as the entire period of time that patients have been taking their prescribed medications and was considered as a continuous variable. Medication class described the category of medications based on their pharmacological target and was treated as a nominal variable. Pill burden represented the total number of medications taken daily and was considered as a continuous variable.

Base, univariate and full (multivariate) models were developed. Each factor of interest was tested individually in a stepwise manner to assess statistical significance of an individual factor on predicted adherence. Models with interaction terms were also considered.

Between study random effects were considered for the intercept as well as factor coefficients. Between study random effects for some factor coefficients were discarded if the model predicted a value that was close to zero. Note here that the random effects were considered nuisance and were considered to reduce
bias in the fixed effects parameters. In all cases between study random effects were included as additive models (as per Equation 2.1).

The residual error model was considered using additive, proportional or combined additive and proportional error models. An additive error model was used for all developed factor models. The first-order conditional estimation with interaction (FOCE + interaction) estimation method was used.

2.3.5. Model selection

Model selection was based on the likelihood ratio test for nested models. The difference of two log likelihoods is asymptotically and approximately chi-squared distributed. Significance for the addition of 1 or more parameters is determined by a decrease in objective function value. The objective function value is proportional to minus twice the log-likelihood. For 1 parameter a difference of more than 3.84 (p-value <0.05) was considered statistically significant. Non-nested models were compared using Akaike’s information criterion (AIC) where decreased values indicate the better fit. Visual plots were performed for the final model to evaluate the goodness of the model fit. The visual plots included plots of observed versus individual predicted adherence percentage, and weighted residual plots.

2.4. Results

A total of 404 papers were initially identified. Figure 2.1 illustrates the study selection and data extraction process. The most commonly studied therapeutic areas were HIV and hypertension. In this work, studies that involved MEMS type devices were selected as it was believed that these studies were likely to provide information on the patterns of adherence rather than less informative overall adherence measures. However, the most commonly recorded adherence criterion was percentage of prescribed doses taken per day. Based on inclusion/exclusion criteria, this adherence criterion and criteria for data extraction, 24 HIV papers and 12 hypertension papers were ultimately included for data extraction.
2.4.1. Data characteristics

Over all 36 papers, the mean age (range) and mean dosing regimen (range) were 45 years (6.9-66.7) and 1.78 (1-4), respectively. Duration of treatment, medication class and pill burden were reported infrequently and could not be considered in this analysis. Note that although patients in studies may receive multiple medications, only selected medication/s were studied and hence used in this analysis.

A summary of data characteristics of the extracted data is shown in Table 2.1. Publication identifier (PID) represented each paper. Study identifier (SID) represented each study being reported within PID. Note that one publication may include more than 1 paper. Consideration of an additional layer of random effects for SID within PID did not improve the model fit. Hence the PID level random effect was not considered further and all studies within a publication were considered to be independent.
Potentially relevant papers identified and screened based on therapeutic areas (n=404)

Based on title and abstract
Papers excluded (n=244)
- Therapeutic areas which contributed less than 10% of the total number of studies

Papers with two selected therapeutic areas retrieved for further evaluation with inclusion criteria (n=160)

HIV (n=103), hypertension (HTN) (n=57)

Based on full text
Papers excluded (n=94): HIV (n=59), HTN (n=35)
- Adherence was not reported from the MEMS. (n=21): HIV (n=19), HTN (n=2)
- The focus of MEMS research was not on reporting adherence results according to defined adherence criterion (further details in text). (n=29): HIV (n=12), HTN (n=17)
- The study reported an intervention (patients being offered adherence education) with no control arms. (n=12): HIV (n=10), HTN (n=2)
- Research that had the same group of patients studied as research that the authors already included. (n=10): HIV (n=7), HTN (n=3)
- The study was a review. (n=7): HIV (n=2), HTN (n=5)
- The study reported methodologies with no results. (n=3): HIV (n=0), HTN (n=3)
- The report was an editorial comment, editorial letter, correspondence. (n=7): HIV (n=5), HTN (n=2)
- Results that were reported did not originate from the research undertaken. (n=1): HIV (n=0), HTN (n=1)
- Only patients with known suboptimal adherence were recruited. (n=1): HIV (n=1), HTN (n=0)
- Study duration was too short (less than 2 weeks). (n=1): HIV (n=1), HTN (n=0)
- The medicines were not a solid dosage form (e.g. liquid medications). (n=2): HIV (n=2), HTN (n=0)

HIV (n=44), HTN (n=22)

Potentially appropriate papers to be considered based on percentage of prescribed does taken per day being used as an adherence criterion (n=66)

Papers with the adherence criterion retrieved (n=51)

HIV (n=37), HTN (n=14)

Based on full text
Papers excluded (n=15): HIV (n=13), HTN (n=2)
- 1) Missing data and could not be imputed based on our assumptions.
- 2) Adherence results were only reported as the proportion of patients with adherence levels i.e. 80% or 95% adherence.

Papers included for data extraction (n=36)

HIV (n=24), HTN (n=12)

Figure 2.1: The study selection and data extraction process
<table>
<thead>
<tr>
<th>Authors</th>
<th>Disease*</th>
<th>PID</th>
<th>SID</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Dosing regimen†</th>
<th>DV#</th>
<th>Mean/Median</th>
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Table 2.1: Data characteristics
Chapter 2: A model-based meta-analysis of the influence of factors that impact on adherence

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<th>Dosing regimen†</th>
<th>DV‡</th>
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</table>
Chapter 2: A model-based meta-analysis of the influence of factors that impact on adherence

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<th>Authors</th>
<th>Disease*</th>
<th>PID</th>
<th>SID</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Dosing regimen†</th>
<th>DV#</th>
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* 0 = hypertension, 1 = HIV † 1 = once daily, 1.5 = once or twice daily, 2 = twice daily, 2.25 = once or twice or thrice daily, 2.5 = twice or thrice daily, 3=thrice daily, 4 = thrice to five times daily PID = publication identifier, SID = study identifier, *DV = dependent variable (% adherence rate)
2.4.2. Influence of disease and other factors on adherence

The base model (without factors) was given by $E[g_{ij}] = 1.89$ which corresponds to an estimated average adherence of 86.88%.

2.4.2.1. Univariate models

Models to assess the influence of disease, age and dosing regimen on adherence are displayed in Table 2.2. Dosing regimen was treated as a continuous value centring by the mean value.

<table>
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<th>Model</th>
<th>Decrease in twice log-likelihood from the base model</th>
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</thead>
<tbody>
<tr>
<td>Disease</td>
<td>$E[g_{ij}] = 2.55 - 0.99 \times DI_{S_{ij}}$</td>
<td>4.95*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$E[g_{ij}] = -0.62 + 2.47 \times AGE_{ij}/45$</td>
<td>1810.20*</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>$E[g_{ij}] = 2.16 - 0.29 \times REG_{ij}/1.78$</td>
<td>680.90*</td>
</tr>
</tbody>
</table>

* $p<0.05$

where $DI_{S_{ij}}$ is disease (0 = hypertension and 1 = HIV) for the $j$th patient in the $i$th study, $AGE_{ij}$ is age (years) for the $j$th patient in the $i$th study and $REG_{ij}$ is dosing regimen treated as a continuous value with 1 = once daily, 2 = twice daily, 3 = thrice daily and so forth for the $j$th patient in the $i$th study.

From given models, the combined influence of disease, age, and dosing regimen on adherence and the corresponding predicted adherence percentage are displayed in Table 2.3. Age values were selected at the interquartile range, 40 and 53 years.

The combined influences of each factor on adherence were: an increase in adherence of 8% per 10 year increase of age, a 4% reduction from once to thrice daily dosing, and that HIV patients were 10% less adherent than hypertension patients.
Table 2.3: Combined influences of an individual factor on adherence with the predicted adherence percentage

<table>
<thead>
<tr>
<th>Factor</th>
<th>$g_{ij}$</th>
<th>Predicted adherence percentage</th>
<th>The difference of two predicted adherence percentage values in sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.55</td>
<td>92.76</td>
<td>-</td>
</tr>
<tr>
<td>HIV</td>
<td>1.56</td>
<td>82.64</td>
<td>10.12</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1.58</td>
<td>82.92</td>
<td>-</td>
</tr>
<tr>
<td>53</td>
<td>2.29</td>
<td>90.80</td>
<td>7.88</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.00</td>
<td>88.08</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.83</td>
<td>86.18</td>
<td>1.90</td>
</tr>
<tr>
<td>3</td>
<td>1.67</td>
<td>84.16</td>
<td>2.02</td>
</tr>
</tbody>
</table>

2.4.2.2. Multivariate models

The final model included all of the factors that were considered. Interaction terms did not contribute significantly to the model fit.

The final model was given by:

$$E[g_{ij}] = \beta_0 + \beta_1 \times DIS_{ij} + \beta_2 \times AGE_{ij}/45 + \beta_3 \times REG_{ij}/1.78$$

*Equation 2.3: The final model*

Parameter estimate values with 95% confidence interval for Equation 2.3 are shown in Table 2.4. Random effects were included on the intercept ($\beta_0$) and $\beta_3$. 

62
Table 2.4: Parameter estimate values with 95% confidence interval for Equation 2.3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
<td>0.26 (-0.08, 0.60)</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.40 (0.15, 0.65)</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>2.43 (2.13, 2.73)</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>-1.10 (-1.47, -0.73)</td>
</tr>
</tbody>
</table>

where $\beta_0$ is intercept, $\beta_1$ is a disease coefficient, $\beta_2$ is an age coefficient and $\beta_3$ is a dosing regimen coefficient.

Table 2.5 shows the adjusted (independent) influence of disease, age, dosing regimen on adherence and the corresponding predicted adherence percentage from the full multivariate model. In this description, age and dosing regimen were fixed at their mean values when calculating predicted adherence percentage for the dosing regimen and age factors, respectively.

The independent influences of each factor on adherence were: an increase in adherence of approximately 8% per 10 year increase of age, a 15-19% reduction from once to thrice daily dosing, and that HIV patients were 5% more adherent than hypertension patients. Note these results were similar to the univariate results except the influence of disease was reversed, and in both circumstances were likely to be of minimal clinical significance.
Table 2.5: Independent influences of each factor on adherence with the predicted adherence percentage

<table>
<thead>
<tr>
<th>Factor</th>
<th>( g_{ij} )</th>
<th>Predicted adherence percentage</th>
<th>The difference of two predicted adherence percentage values in sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.59</td>
<td>83.06</td>
<td>-</td>
</tr>
<tr>
<td>HIV</td>
<td>1.99</td>
<td>87.97</td>
<td>4.91</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1.32</td>
<td>78.92</td>
<td>-</td>
</tr>
<tr>
<td>53</td>
<td>2.02</td>
<td>88.29</td>
<td>9.37</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1.72</td>
<td>84.81</td>
<td>-</td>
</tr>
<tr>
<td>53</td>
<td>2.42</td>
<td>91.83</td>
<td>7.02</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.07</td>
<td>88.80</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.45</td>
<td>81.00</td>
<td>7.8</td>
</tr>
<tr>
<td>3</td>
<td>0.84</td>
<td>69.85</td>
<td>11.15</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.47</td>
<td>92.20</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.85</td>
<td>86.41</td>
<td>5.79</td>
</tr>
<tr>
<td>3</td>
<td>1.24</td>
<td>77.56</td>
<td>8.85</td>
</tr>
</tbody>
</table>
The relationship between dosing regimen, age and predicted adherence percentage is illustrated in the surface plots, Figure 2.2.

**Figure 2.2:** Predicted adherence percentage for HIV patients (a) and hypertension patients (b). In these plots dosing regimen is shown on the x-axis (1 denotes once daily, 2 twice daily and so forth), age (years) on the y-axis and predicted adherence on the z-axis.

The surface plots provide an overall interpretation of the strength and direction of the influence of various factors on adherence. Overall, HIV patients demonstrated slightly higher predicted adherence percentage compared to hypertension patients. It is clear from the surface plots that the influence of age is the most significant factor of interest. In both HIV and hypertension there is a clear decline in adherence with decreasing age (note this should only be interpreted over the age ranges included in this analysis). Dosing regimen while also significant showed a consistent but less dramatic decline in adherence with increasing dosing regimen complexity (up to four times daily). Since no interactions were identified between the factors considered then these effects were consistent across bands of age and dosing regimen. It is also observable from the surface plots that dosing regimen (from once to thrice daily) while reducing adherence in the older age group did not reduce adherence below approximately 80%. However in younger age groups (e.g. 40 years) the influence of complex regimens (multiple daily doses) may result in adherence that is poor.
Diagnostic plots are provided in Appendix A.1.2. Weighted residual plots of disease, age and dosing regimen showed that there was no trend in the weighted residual plots. Some studies were outside the range of -5, 5. This may be due to several reasons such as unbalanced designs of the studies or some observations being unique from others.

2.5. Discussion

A variety of factors influencing adherence has been studied in chronic diseases. However, to our knowledge, the independent influence of different diseases on adherence has not been addressed. This study used a MBMA technique which allows determination of the independent influence of disease on adherence once other factors, namely age and dosing regimen have been taken into account. In addition, the independent influence of these other factors was determined. Random effects which allowed for between study variability and residual unexplained variability were considered. This MBMA technique was used in the study by Ito et al. where an Alzheimer’s disease progression model was developed based on literature [138]. It was also used in other studies with various therapeutic areas including migraine, rheumatoid arthritis and diabetes [137, 139, 140].

The four key findings of this work are the independent influences of age, dosing regimen and disease on adherence (in order of importance). Namely: (1) adherence improves with increasing age, (2) dosing regimen negatively influences adherence in a linear manner (i.e. twice daily dosing is associated with a decreased adherence of 6-8% compared to once daily dosing), (3) disease, in terms of hypertension compared to HIV has a modest effect on adherence and (4) the importance of dosing regimen on adherence wanes with advancing age (based on the surface plots), in the sense that although increased complexity of the dosing regimen decreases adherence the base level of adherence in (for example) a 60 year olds is considerably better than 40 year olds and hence the influence may be of less importance.
Our findings indicate that increasing age has a positive influence on adherence which corresponds to previous studies [97, 169-172]. An adherence study of patients with hyperlipidaemia has shown that the group of patients at a mean age of 56 years were better adherent compared to those at a mean age of 47 years [172]. However, in other studies no relationship between age and adherence has been found [173-176]. The reason for these conflicting findings is unknown but may be explained by study design and patient related factors. In terms of study design it would be needed for at least a two decade difference in the mean ages between the cohorts to expect to see a 15-20% difference in adherence and hence many studies may be underpowered to detect differences. Regarding lifestyle, the underlying premise that older patients tend to have simpler more ordered life styles which may allow them to pay greater attention to and set their medication taking as a daily routine contrasts with younger and middle-aged patients who often have busy life-styles that may affect their adherence [177, 178]. It has also been reported that declining cognitive function with age in the very old may accompany decreased adherence [171, 177, 179]. The impact of age-related cognitive function on adherence remains unanswered here because some studies initially excluded patients with cognitive deterioration during recruitment process and cognitive impairment was not available as a factor in this study. However, Park et al. proposed that although a decline in cognitive function was related to age, the effect was insufficient to hamper adherence in the elderly [178]. The concern with declined cognitive impairment may also be related to a decline in health literacy which may affect adherence but, and importantly, various medication pack devices exist that can help organise medicines and improve adherence and do not require a high level of health literacy. Ultimately, the more worrying target may well be middle-aged or younger patients.

Our findings should be considered with caution at the extremes of age included in this study (i.e. 7 and 67 years). In particular paediatric patients are likely to have a carer administering the medicines and hence adherence has an entirely different context. Importantly also this study does not elucidate factors
that affect adherence in the elderly (over 70 year olds) and further work in this group is required. Based on a general assumption that patients of older age may be expected to be more non-adherent, due to various barriers such as multiple chronic diseases with multiple medications and/or the large number of medications and supposed cognitive dysfunction, it seems that older patients have been the main focus for clinical adherence support [45]. Although the importance of an advanced age related decline in adherence in this exploratory work cannot be ruled out, it seems that adherence support services should also consider younger age cohorts.

The finding that dosing regimen negatively influences adherence in a linear manner is not surprising. Numerous studies have investigated the influence of implementing a dosing regimen on adherence across a variety of chronic diseases. A general consensus is implementing higher frequency of doses per day reduces the adherence level [119, 120]. These values were however, perhaps surprisingly, less significant than age in this current study.

The influence of disease on adherence has been reported to be insignificant [58, 180]. A review of published studies by Haynes et al. [30], before 1978, identified three issues 1) patients with psychiatric diseases are likely to exhibit lower levels of adherence. 2) poorer adherence may be associated with of greater numbers of symptoms. 3) higher adherence may be resulted from higher level of disability. Urquhart et al. suggested that poor adherence with delayed and missed doses in the implementation phase shared similarities across different diseases [58]. This work considered, glaucoma, epilepsy and ankylosing spondylitis. The authors also concluded that symptoms, prognoses and medications did not appear to affect adherence [58]. Another study by DiMatteo compared mean adherence across 17 studies with the range of disease severity and asymptomatic or symptomatic conditions including HIV, cardiovascular diseases, cancer, diabetes and gastrointestinal disorders [180]. Their findings demonstrated that variability across mean adherence scores were not significant. In this current work, it was found that disease was statistically significant, however the influence appeared to be slight compared to other factors.
Interestingly in this work, in the univariate analysis patients with hypertension were found to be more adherent than HIV patients however this was reversed in the full multivariate model. The final model identified the independent influence of disease on adherence was statistically significant with HIV patients being on average 5% more adherent than patients with hypertension.

The influence of pill burden on adherence was one of the factors of interest. However, little data were reported on the total number of medications patients taking per day. Therefore, this factor could not be considered in this analysis. It is likely that this may well be correlated with age and hence our findings on age should be viewed as exploratory until more fully investigated. Similarly, due to poor reporting of other factors including duration of treatment, caution is advised regarding confounding effects.

There are a number of limitations to this study. Firstly, only two therapeutic areas were studied, due to the availability of published data. Therefore, conclusions about the importance of disease as an influence on adherence are only in the context of hypertension and HIV. Secondly, it is surprising that the most commonly used adherence criterion in MEMS studies was the percentage of prescribed doses taken per day. This is a blunt criterion and hides the impact of patterns of adherence. Due to limited literature, it was not possible to use a more appropriate criterion and therefore our study should be perceived as a first attempt to quantify the independent influence of factors on adherence. It is likely that the results could be different when further data available. It is recommended that future MEMS studies should report not only summary statistics about adherence, such as percent of doses taken, but also report numbers of missed doses, drug holidays, timing variability as well as initiation and discontinuation issues. Thirdly, there was a need for imputation of missing data, namely number of patients, disease, age, dosing regimen and adherence results. Since retrieved adherence papers were those using MEMS, the aims of the individual papers varied widely. Therefore the required data for our data extraction regarding factors influencing adherence were not always provided. This meta-analysis combined studies with different goals and hence is exploratory in nature rather
than providing high level evidence. Finally, since individual level data were not obtainable from all studies then each individual was imputed at the mean of the population stratified for the dosing regimen and disease. This last limitation has significant implications as the results of the influence of various factors will be limited to information in the means and generally not by individual responses. It is believed that this is likely to decrease the size of the influence of the factors due to regression to the mean. Conclusions regarding the absolute influence of age and dosing regimen should be treated with caution, but it seems reasonable that the effects found in this study may probably be conservative and underestimate the true influence of these factors.

2.6. Conclusions

This study considers the influence of various factors on adherence in a multivariate analysis comparing and contrasting adherence from two different diseases. While the influence of disease on adherence was significant it is likely to be of limited clinical significance. Adherence appears to improve with age and decline with the greater frequency of dosing regimen. Additionally, the influence of dosing regimen wanes with increasing age. These results should be treated as exploratory and require prospective assessment.
Chapter 3: Measures of adherence in the Medication Event Monitoring System literature
3.1. Context

It was thought that the use of Medication Event Monitoring System (MEMS) would confer an advantage over other adherence measurements in that it provides data on actual adherence patterns i.e. temporal patterns, which are a crucial element to understand the impact of types of imperfect adherence on dose-response relationship. As found in Chapter 2, it was however unexpected that although MEMS type devices are widely used, studies in general limited their account of adherence to global measures (i.e. pill counts) and on the whole did not report patterns of adherence. This means that much of the reported MEMS adherence data fail to provide information that would provide an understanding of the adherence patterns that would yield a specific fractional adherence, e.g. 60% of doses taken.

In 1997, the work of Kastrissios and Blaschke [110] demonstrated various reported adherence measures in MEMS literature. The most commonly reported adherence measures were percentage of doses taken and percentage of days with correct doses. Other adherence measures used were percentage of doses taken on schedule, therapeutic coverage and duration and frequency of drug holidays [110]. The work of Vrijens et al. in 1997 [181] determined six possible ways to measure adherence. The first three adherence measures considered the level of the number of doses: 1) percentage of days with correct doses, 2) percentage of doses taken and 3) percentage of drug holidays. The latter three adherence measures considered the level of the timing of doses: 4) timing variability of doses taken, 5) percentage of too short or too long dosing intervals and 6) median and quartiles of dosing intervals [181]. This work of Vrijens et al. [181] has provided an initial approach of measuring adherence for MEMS studies with the consideration of dose timing data.

The importance of dose timing data has been reiterated by Blaschke et al. in 2012 who reported examples of four patients with acceptable adherence over one year (90% of average prescribed doses taken) [54]. However, these four cases showed various chronological patterns of imperfect adherence including
delayed initiation, early discontinuation, random missed doses and drug holidays [54].

Further to the work of Kastrissios and Blaschke in 1997 [110], an overview of various adherence measures used in MEMS studies of commonly studied therapeutic areas, described in Chapter 2 as HIV and hypertension, has not been investigated.

3.2. Aims

The aims of this study are:

(1) To develop a set of categories of adherence measures based on those reported in MEMS studies.

(2) To illustrate adherence measures.

(3) To investigate the frequency of the use of various adherence measures in MEMS studies in HIV and hypertension therapeutic areas.

(4) To propose aggregate adherence measures for future MEMS studies. This will be used in Chapter 4.

For ease of reading, aims (1) and (2) will be discussed in the methods section while aim (3) will be discussed in the results section and aim (4) will be discussed in the discussion section.

3.3. Methods

MEMS studies used in this study were those retrieved after exclusion criteria had been applied in Chapter 2. Please refer to Figure 2.1: the study selection and data extraction process in Chapter 2. There were 66 papers (44 HIV papers and 22 hypertension papers) included prior to the most commonly recorded adherence criterion being used to filter studies (see Table 3.1 and Table 3.2 for a summary). The retrieved studies were from the years 1998 to 2011. A review of possible adherence measures used in those 66 papers was conducted. Documented adherence measures were then categorised and illustrated.
### Table 3.1: A summary of HIV papers included for this study

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frick et al. [155]</td>
<td>1998</td>
<td>AIDS Patient Care STDS</td>
<td>Antiretroviral medication compliance in patients with AIDS</td>
</tr>
<tr>
<td>Kastrissios et al. [97]</td>
<td>1998</td>
<td>AIDS</td>
<td>Characterizing patterns of drug-taking behavior with a multiple drug regimen in an AIDS clinical trial</td>
</tr>
<tr>
<td>Melbourne et al. [73]</td>
<td>1999</td>
<td>AIDS Read</td>
<td>Medication adherence in patients with HIV infection: a comparison of two measurement methods</td>
</tr>
<tr>
<td>Gross et al. [182]</td>
<td>2001</td>
<td>AIDS</td>
<td>Effect of adherence to newly initiated antiretroviral therapy on plasma viral load</td>
</tr>
<tr>
<td>Liu et al. [160]</td>
<td>2001</td>
<td>Ann Intern Med</td>
<td>A comparison study of multiple measures of adherence to HIV protease inhibitors</td>
</tr>
<tr>
<td>McNabb et al. [183]</td>
<td>2001</td>
<td>Clin Infect Dis</td>
<td>Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic</td>
</tr>
<tr>
<td>Hinkin et al. [156]</td>
<td>2002</td>
<td>Neurology</td>
<td>Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity</td>
</tr>
<tr>
<td>Howard et al. [158]</td>
<td>2002</td>
<td>AIDS</td>
<td>A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women</td>
</tr>
<tr>
<td>Hugen et al. [184]</td>
<td>2002</td>
<td>J Acquir Immune Defic Syndr</td>
<td>Assessment of adherence to HIV protease inhibitors: comparison and combination of various methods, including MEMS (electronic monitoring), patient and nurse report, and therapeutic drug monitoring</td>
</tr>
<tr>
<td>Ickovics et al. [159]</td>
<td>2002</td>
<td>J Acquir Immune Defic Syndr</td>
<td>Prenatal and postpartum zidovudine adherence among pregnant women with HIV: results of a MEMS substudy from the Perinatal Guidelines Evaluation Project</td>
</tr>
<tr>
<td>Mathews et al. [185]</td>
<td>2002</td>
<td>AIDS Patient Care STDS</td>
<td>Prevalence, predictors, and outcomes of early adherence after starting or changing antiretroviral therapy</td>
</tr>
<tr>
<td>Wagner [186]</td>
<td>2002</td>
<td>AIDS Patient Care STDS</td>
<td>Predictors of antiretroviral adherence as measured by self-report, electronic monitoring, and medication diaries</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Journal</td>
<td>Title</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------</td>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wagner et al. [94]</td>
<td>2003</td>
<td>AIDS Patient Care STDs</td>
<td>Adherence to HIV antiretrovirals among persons with serious mental illness</td>
</tr>
<tr>
<td>Berg et al. [188]</td>
<td>2004</td>
<td>J Gen Intern Med</td>
<td>Gender differences in factors associated with adherence to antiretroviral therapy</td>
</tr>
<tr>
<td>Weber et al. [168]</td>
<td>2004</td>
<td>Antivir Ther</td>
<td>Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial</td>
</tr>
<tr>
<td>de Bruin et al. [189]</td>
<td>2005</td>
<td>AIDS Patient Care STDs</td>
<td>Theory- and evidence-based intervention to improve adherence to antiretroviral therapy among HIV-infected patients in the Netherlands: a pilot study</td>
</tr>
<tr>
<td>Fletcher et al. [154]</td>
<td>2005</td>
<td>J Acquir Immune Defic Syndr</td>
<td>Four measures of antiretroviral medication adherence and virologic response in AIDS clinical trials group study 359</td>
</tr>
<tr>
<td>Weaver et al. [190]</td>
<td>2005</td>
<td>Health Psychol</td>
<td>A stress and coping model of medication adherence and viral load in HIV-positive men and women on highly active antiretroviral therapy (HAART)</td>
</tr>
<tr>
<td>Levine et al. [69]</td>
<td>2006</td>
<td>Health Psychol</td>
<td>Adherence to antiretroviral medications in HIV: differences in data collected via self-report and electronic monitoring</td>
</tr>
<tr>
<td>Bell et al. [150]</td>
<td>2007</td>
<td>J Acquir Immune Defic Syndr</td>
<td>Adherence to antiretroviral therapy in patients receiving free treatment from a government hospital in Blantyre, Malawi</td>
</tr>
<tr>
<td>Hinkin et al. [191]</td>
<td>2007</td>
<td>AIDS Behav</td>
<td>Drug use and medication adherence among HIV-1 infected individuals</td>
</tr>
<tr>
<td>Molina et al. [161]</td>
<td>2007</td>
<td>AIDS Res Hum Retroviruses</td>
<td>A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks</td>
</tr>
<tr>
<td>Munoz-Moreno et al. [70]</td>
<td>2007</td>
<td>AIDS Res Hum Retroviruses</td>
<td>Assessing self-reported adherence to HIV therapy by questionnaire: the SERAD (Self-Reported Adherence) Study</td>
</tr>
<tr>
<td>Parienti et al. [162]</td>
<td>2007</td>
<td>AIDS</td>
<td>Effect of twice-daily nevirapine on adherence in HIV-1-infected patients: a randomized controlled study</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Journal</td>
<td>Title</td>
</tr>
<tr>
<td>--------------------</td>
<td>------</td>
<td>--------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Shuter et al. [166]</td>
<td>2007</td>
<td>J Acquir Immune Defic Syndr</td>
<td>HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%</td>
</tr>
<tr>
<td>Boyle et al. [151]</td>
<td>2008</td>
<td>HIV Clin Trials</td>
<td>Randomization to once-daily stavudine extended release/lamivudine/efavirenz versus a more frequent regimen improves adherence while maintaining viral suppression</td>
</tr>
<tr>
<td>Gross et al. [193]</td>
<td>2008</td>
<td>HIV Clin Trials</td>
<td>How long is the window of opportunity between adherence failure and virologic failure on efavirenz-based HAART?</td>
</tr>
<tr>
<td>Lu et al. [194]</td>
<td>2008</td>
<td>AIDS Behav</td>
<td>Optimal recall period and response task for self-reported HIV medication adherence</td>
</tr>
<tr>
<td>Maitland et al. [95]</td>
<td>2008</td>
<td>HIV Med</td>
<td>Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy</td>
</tr>
<tr>
<td>Patierti et al. [163]</td>
<td>2008</td>
<td>PLoS ONE</td>
<td>Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels</td>
</tr>
<tr>
<td>Vranceanu et al. [195]</td>
<td>2008</td>
<td>AIDS Patient Care STDs</td>
<td>The relationship of post-traumatic stress disorder and depression to antiretroviral medication adherence in persons with HIV</td>
</tr>
<tr>
<td>Applebaum et al. [196]</td>
<td>2009</td>
<td>AIDS Patient Care STDs</td>
<td>The impact of neuropsychological functioning on adherence to HAART in HIV-infected substance abuse patients</td>
</tr>
<tr>
<td>Ettenhofer et al. [152]</td>
<td>2009</td>
<td>Am J Geriatr Psychiatry</td>
<td>Aging, neurocognition, and medication adherence in HIV infection</td>
</tr>
<tr>
<td>Shuter et al. [167]</td>
<td>2009</td>
<td>HIV Clin Trials</td>
<td>Occurrence of selective ritonavir nonadherence and dose-staggering in recipients of boosted HIV-1 protease inhibitor therapy</td>
</tr>
<tr>
<td>Haberer et al. [198]</td>
<td>2011</td>
<td>PLoS ONE</td>
<td>Excellent adherence to antiretrovirals in HIV+ Zambian children is compromised by disrupted routine, HIV nondisclosure, and paradoxical income effects</td>
</tr>
</tbody>
</table>
### Table 3.2: A summary of hypertension papers included for this study

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mengden et al. [143]</td>
<td>1993</td>
<td>J Hypertens</td>
<td>The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening</td>
</tr>
<tr>
<td>Kruse et al. [142]</td>
<td>1994</td>
<td>Int J Clin Pharmacol Ther</td>
<td>Patterns of drug compliance with medications to be taken once and twice daily assessed by continuous electronic monitoring in primary care</td>
</tr>
<tr>
<td>Leenen et al. [93]</td>
<td>1997</td>
<td>Can J Cardiol</td>
<td>Patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care: a randomized clinical trial using electronic monitoring</td>
</tr>
<tr>
<td>Choo et al. [141]</td>
<td>1999</td>
<td>Med Care</td>
<td>Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy</td>
</tr>
<tr>
<td>Svarstad et al. [146]</td>
<td>1999</td>
<td>Patient Educ Couns</td>
<td>The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence</td>
</tr>
</tbody>
</table>
Chapter 3: Measures of adherence in the Medication Event Monitoring System literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrejak et al. [125]</td>
<td>2000</td>
<td>Am J Hypertens</td>
<td>Electronic pill-boxes in the evaluation of antihypertensive treatment compliance: comparison of once daily versus twice daily regimen</td>
</tr>
<tr>
<td>Burnier et al. [201]</td>
<td>2001</td>
<td>J Hypertens</td>
<td>Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions</td>
</tr>
<tr>
<td>Wetzels et al. [147]</td>
<td>2006</td>
<td>BMC Health Serv Res</td>
<td>All that glisters is not gold: a comparison of electronic monitoring versus filled prescriptions—an observational study</td>
</tr>
<tr>
<td>Wetzels et al. [203]</td>
<td>2007</td>
<td>Am J Hypertens</td>
<td>Electronic monitoring of adherence as a tool to improve blood pressure control. A randomized controlled trial</td>
</tr>
<tr>
<td>Bogner and de Vries [204]</td>
<td>2008</td>
<td>Ann Fam Med</td>
<td>Integration of depression and hypertension treatment: a pilot, randomized controlled trial</td>
</tr>
<tr>
<td>Braam et al. [205]</td>
<td>2008</td>
<td>Br J Clin Pharmacol</td>
<td>Bromide as marker for drug adherence in hypertensive patients</td>
</tr>
<tr>
<td>Zeller et al. [148]</td>
<td>2008</td>
<td>J Clin Epidemiol</td>
<td>An adherence self-report questionnaire facilitated the differentiation between nonadherence and nonresponse to antihypertensive treatment</td>
</tr>
<tr>
<td>Zeller et al. [149]</td>
<td>2008</td>
<td>Hypertens Res</td>
<td>Physicians’ ability to predict patients’ adherence to antihypertensive medication in primary care</td>
</tr>
<tr>
<td>Zeller et al. [75]</td>
<td>2008</td>
<td>Hypertens Res</td>
<td>Patients’ self-reported adherence to cardiovascular medication using electronic monitors as comparators</td>
</tr>
<tr>
<td>Ruppar [207]</td>
<td>2010</td>
<td>J Cardiovasc Nurs</td>
<td>Randomized pilot study of a behavioral feedback intervention to improve medication adherence in older adults with hypertension</td>
</tr>
<tr>
<td>Rose et al. [209]</td>
<td>2011</td>
<td>J Clin Hypertens</td>
<td>Effects of daily adherence to antihypertensive medication on blood pressure control</td>
</tr>
</tbody>
</table>
3.3.1. **Categorisation of adherence measures used in MEMS studies**

Documented adherence measures comprised a variety of adherence measures across MEMS studies. In addition, multiple adherence measures were used in some studies. Therefore, relevant adherence measures were identified and subsequently grouped together. Ultimately, based on grouped relevant adherence measures, the categorisation of adherence measures was developed as the following 6 main categories:

1. the main category of doses taken
2. the main category of missed doses
3. the main category of extra doses taken
4. the main category of timing
5. the main category of the impact of drug taking on drug effects
6. other categories

Each main category comprises its categories with relevant sub-categories as shown in sections 3.3.1.1 to 3.3.1.6.

Note the purpose of this work was not to propose categories for adherence measures that hold particular clinical meaning but rather to report the typical categories that the MEMS literature supports. Therefore, it is expected that there may be overlap between some sub-categories within a particular category; and that certain main categories may seem incomplete.
3.3.1.1. The main category of doses taken

The main category of doses taken begins with a broad category: only the number of doses taken is counted, followed by a category counting the number of doses taken at a day level, and finally the number of doses taken with timing being considered.

- **Category 1 (C1)**: Number of doses taken
- **Category 2 (C2)**: Number of days with doses taken
  - **Category 2.1 (C2.1)**: Number of days with correct doses
  - **Category 2.2 (C2.2)**: Number of days with correct dosing
  - **Category 2.3 (C2.3)**: Number of days with 2 correct dosing intervals in 3 dosing intervals

Correct doses in C2.1 refers to the correct number of doses taken whereas correct dosing in C2.2 refers to the correct number of doses taken as well as the correct dosing interval. C2.3 is treated separately from C2.2 when only 2 correct dosing intervals out of 3 dosing intervals is considered, but not 3 correct dosing intervals in 3 dosing intervals.

For C3 and C4, they involve both the number of doses taken and timing elements where C3 considers when a dose is taken appropriately and C4 considers when a dose is taken beyond an appropriate interval.

- **Category 3 (C3)**: Number of doses taken on schedule
- **Category 4 (C4)**: Number of delayed doses

3.3.1.2. The main category of missed doses

The main category of missed doses has a similar structure as the main category of doses taken. It begins with the number of missed doses, followed by the number of missed doses with timing being considered and finally the consecutive days of missed doses.

- **Category 5 (C5)**: Number of missed doses
- **Category 6 (C6)**: Number of missed doses within defined intervals
- **Category 7 (C7)**: Number of missed doses at a day level
Chapter 3: Measures of adherence in the Medication Event Monitoring System literature

C7.1 considers how many days in a prescribed period that at least one dose is missed for daily dosing, while C7.2 covers the number of days where only 1 dose is taken for twice daily dosing.

- Category 7.1 (C7.1) Number of days with missed doses
- Category 7.2 (C7.2) Number of days with 1 missed dose for twice daily dosing

C7.3 to C7.9 consider how many consecutive days where missed doses occur. The definition of consecutive days with missed doses ranges from 1 day to 7 days.

- Category 7.3 (C7.3) Number of days with missed doses for 1 day
- Category 7.4 (C7.4) Number of days with missed doses for 1-2 days
- Category 7.5 (C7.5) Number of days with missed doses for 2 days
- Category 7.6 (C7.6) Number of days with missed doses for at least 2 days
- Category 7.7 (C7.7) Number of days with missed doses for 3 days
- Category 7.8 (C7.8) Number of days with missed doses for 7 days
- Category 7.9 (C7.9) Longest number of days with missed doses

3.3.1.3. The main category of extra doses taken

This main category of extra doses taken looks at the number of extra doses taken at a day level.

- Category 8 (C8) Number of days with extra doses taken
3.3.1.4. The main category of timing

This main category of timing summarises reported measures considering solely the level of timing, which is different from the previous defined categories. Those considered the level of timing in conjunction with the number of doses taken or the number of missed doses.

**Category 9 (C9) Timing**

C9.1 covers the longest possible timing errors that could occur between doses.

**Category 9.1 (C9.1)** The duration of the longest intervals between doses

**Category 9.2 (C9.2)** Mode of hour distributions

C9.2 is where the mode of hour distributions is defined as the hour at which the drug is taken most frequently.

**Category 9.3 (C9.3)** Coefficient of variation

C9.3 is where the coefficient of variation is defined as (standard deviation of the timing between doses divided by mean timing between doses) x 100%.

**Category 9.4 (C9.4)** The proportion of timing of doses taken within correct timing intervals

C9.4 is similar to C3, the number of doses taken on schedule. Here it is viewed as the percentage of correct timing over a prescribed period.

**Category 9.5 (C9.5)** Sum of the interval of timing between doses divided by the number of MEMS openings

C9.5 considers the average of timing errors between doses over a prescribed period.
3.3.1.5. The main category of the impact of drug taking on drug effects

This main category of the impact of drug taking on drug effects further looks at therapeutic attainment in addition to how patients take drugs described in the previous 3 main categories.

<table>
<thead>
<tr>
<th>Category 10 (C10)</th>
<th>The impact of drug taking on drug effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 10.1 (C10.1)</td>
<td>Therapeutic coverage</td>
</tr>
<tr>
<td>Category 10.2 (C10.2)</td>
<td>Uncovered time in 24 hours for once and twice daily dosing</td>
</tr>
</tbody>
</table>

C10.1 looks at the duration that the drug effect is covered given the doses that were taken, and C10.2 is another perspective of measuring uncovered time, in the case of once and twice daily dosing.

3.3.1.6. Other categories

These include categories which do not fit into the above 4 main categories.

<table>
<thead>
<tr>
<th>Category 11 (C11)</th>
<th>Other categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 11.1 (C11.1)</td>
<td>Number of days with equal or greater than one dose being taken</td>
</tr>
<tr>
<td>Category 11.2 (C11.2)</td>
<td>Number of doses taken divided by number of prescribed days</td>
</tr>
</tbody>
</table>
3.3.2. Illustration of adherence measures

The main categories of dose taken, missed doses and extra doses taken are illustrated here using a diagram of thrice, twice and once daily dosing where appropriate.

3.3.2.1. The main category of doses taken

*Table 3.3:* Illustration of the main category of doses taken. The red colour identifies where each scenario occurs.

<table>
<thead>
<tr>
<th>Category*</th>
<th>Thrice daily</th>
<th>Twice daily</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 Number of doses taken</td>
<td>● X X</td>
<td>● X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● X</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>7/9</td>
<td>4/6</td>
<td>2/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C2 Number of days with doses taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2.1 Number of days with correct doses</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| C2.2 Number of days with correct dosing | ● ↔ X ↔ X | ● ↔ X | X |
| | ● ↔ ● ↔ ● | ● ↔ ● | ● |
| | ● ↔ ● ------ ● | ● ------ ● | ● |
| | 1/3 | 1/3 | 2/3 |

<p>| C2.3 Number of days with 2 correct dosing intervals in 3 dosing intervals | Case 1 | N/A | N/A |
| | ● ↔ X ↔ X | ● ↔ X | X |
| | ● ↔ ● ← ● | ● ↔ ● ← ● |
| | 1/3 | 1/3 | 2/3 |</p>
<table>
<thead>
<tr>
<th>Category*</th>
<th>Thrice daily</th>
<th>Twice daily</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2.3 Number of days with 2 correct dosing intervals in 3 dosing intervals</td>
<td>Case 2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>● ↔ X ↔ X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● ↔ ● ↔ X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● ↔ ● ------ ●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3 Number of doses taken on schedule</td>
<td>● ↔ X ↔ X</td>
<td>X ↔ X</td>
<td>X</td>
</tr>
<tr>
<td>● ↔ ● ↔ ●</td>
<td>● ↔ ●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>● ↔ ● ------ ●</td>
<td>● ------ ●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>6/9</td>
<td>3/6</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>e.g. ±25%</td>
<td>e.g. ±25%</td>
<td>e.g. ±25%</td>
<td></td>
</tr>
<tr>
<td>● ↔ ● =</td>
<td>● ↔ ● =</td>
<td>● ↔ ● =</td>
<td></td>
</tr>
<tr>
<td>8±2 hour</td>
<td>12±3 hours</td>
<td>24±6 hours</td>
<td></td>
</tr>
<tr>
<td>C4 Number of delayed doses</td>
<td>● ↔ X ↔ X</td>
<td>X ↔ X</td>
<td>X</td>
</tr>
<tr>
<td>● ↔ ● ↔ ●</td>
<td>● ↔ ●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>● ↔ ● ------ ●</td>
<td>● ------ ●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>1/9</td>
<td>1/6</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td>e.g. ± &gt;25%</td>
<td>e.g. ± &gt;25%</td>
<td>e.g. ± &gt;25%</td>
<td></td>
</tr>
<tr>
<td>● ------ ● =</td>
<td>● ------ ● =</td>
<td>● ------ ● =</td>
<td></td>
</tr>
<tr>
<td>8± &gt;2 hour</td>
<td>12± &gt;3 hours</td>
<td>24± &gt;6 hours</td>
<td></td>
</tr>
</tbody>
</table>

(* Expressed in Number, Percentage, Proportion)

● = taken doses
X = missed doses
↔ = acceptable interval between days and doses
------ = unacceptable interval

Note intervals between days are acceptable unless otherwise stated.
3.3.2.2. The main category of missed doses

**Table 3.4:** Illustration of the main category of missed doses. The red colour identifies where each scenario occurs.

<table>
<thead>
<tr>
<th>Category*</th>
<th>Thrice daily</th>
<th>Twice daily</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C5 Number of missed doses</strong></td>
<td>● XX</td>
<td>● X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>2/9</td>
<td>1/6</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>C6 Number of missed doses</strong></td>
<td>● ↔ X ↔ X</td>
<td>● ↔ X</td>
<td>X</td>
</tr>
<tr>
<td>within defined intervals</td>
<td>● ↔ ● ↔ ●</td>
<td>● ↔ ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>● ↔ ● —— ●</td>
<td>● —— ●</td>
<td>●</td>
</tr>
<tr>
<td>e.g. ±25%</td>
<td>e.g. ±25%</td>
<td>e.g. ±25%</td>
<td></td>
</tr>
<tr>
<td>X ↔ X =</td>
<td>X ↔ X =</td>
<td>X ↔ X =</td>
<td></td>
</tr>
<tr>
<td>8±2 h</td>
<td>12±3 h</td>
<td>24±6 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/9</td>
<td>1/6</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>C7 Number of missed doses in days (Number of drug holidays)</strong></td>
<td>● ↔ X ↔ X</td>
<td>● ↔ X</td>
<td>X</td>
</tr>
<tr>
<td><strong>C7.1 Number of days with missed doses</strong></td>
<td>● ↔ ● ↔ ●</td>
<td>● ↔ ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>● ↔ ● —— ●</td>
<td>● —— ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>C7.2 Number of days with 1 missed dose for twice daily dosing</strong></td>
<td>N/A</td>
<td>● ↔ X</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>● ↔ ●</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>● —— ●</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C7.3 Number of days with missed doses for 1 day</strong></td>
<td>XXX</td>
<td>XX</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
</tr>
</tbody>
</table>
### Measures of adherence in the Medication Event Monitoring System literature

<table>
<thead>
<tr>
<th>Category*</th>
<th>Thrice daily</th>
<th>Twice daily</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C7.4 Number of days with missed doses for 1-2 days</strong></td>
<td>● ● ●</td>
<td>● ●</td>
<td>● ● ●</td>
</tr>
<tr>
<td>Possible Case 1: All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td><strong>C7.4 Number of days with missed doses for 1-2 days</strong></td>
<td>● ● ●</td>
<td>● ●</td>
<td>● ● ●</td>
</tr>
<tr>
<td>Possible Case 2: All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td><strong>C7.5 Number of days with missed doses for 2 days</strong></td>
<td>● ● ●</td>
<td>● ●</td>
<td>● ● ●</td>
</tr>
<tr>
<td>All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td><strong>C7.6 Number of days with missed doses for at least 2 days</strong></td>
<td>● ● ●</td>
<td>● ●</td>
<td>● ● ●</td>
</tr>
<tr>
<td>Possible Case 1: All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td>Possible Case 2: All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td><strong>C7.7 Number of days with missed doses for 3 days</strong></td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td>All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td><strong>C7.8 Number of days with missed doses for 7 days</strong></td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td>All counted as 1</td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
<tr>
<td></td>
<td>X X X</td>
<td>X X</td>
<td>X X X</td>
</tr>
</tbody>
</table>
(Previous page)

(*Expressed in Number, Percentage, Proportion)

● = taken doses
X = missed doses
↔ = acceptable interval between days and doses
------ = unacceptable interval

Note intervals between days are acceptable unless otherwise stated

3.3.2.3. The main category of extra doses taken

**Table 3.5: Illustration of the main category of extra doses taken. The red dot represents an extra dose taken.**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Thrice daily</th>
<th>Twice daily</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8 Number of days with extra doses taken</td>
<td>● X X</td>
<td>● X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>● ● ●</td>
<td>● ●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>● ● ● ●</td>
<td>● ● ●</td>
<td>● ●</td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
</tr>
</tbody>
</table>

(*Expressed in Number, Percentage, Proportion)

● = taken doses
X = missed doses
↔ = acceptable interval between days and doses
------ = unacceptable interval

Note intervals between days are acceptable unless otherwise stated
3.4. Results

The frequency of the use of each adherence measure, C1-C11 is presented in this section. A total of 66 MEMS papers were included in this study (44 HIV papers and 22 hypertension papers). Note here that in some studies, more than one adherence measure was used within a study.

3.4.1. The main category of doses taken

The number of MEMS studies using C1, C2 and C4 are presented in Table 3.6. Those using C3 are shown in Table 3.7 with an explanation of how dosing intervals were defined in order for them to be considered as having been taken on schedule.

**Table 3.6: MEMS studies using C1, C2 and C4**

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td><strong>C1 Number of doses taken</strong></td>
<td>38</td>
</tr>
<tr>
<td><strong>C2 Number of days with doses taken</strong></td>
<td></td>
</tr>
<tr>
<td>C2.1 Number of days with correct doses</td>
<td>11</td>
</tr>
<tr>
<td>C2.2 Number of days with correct dosing</td>
<td>3</td>
</tr>
<tr>
<td>C2.3 Number of days with 2 correct dosing</td>
<td>-</td>
</tr>
<tr>
<td>C2.4 Number of days with 3 correct dosing</td>
<td>-</td>
</tr>
<tr>
<td><strong>C4 Number of delayed doses</strong></td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3.7: MEMS studies using C3

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C3 Number of doses taken on schedule</strong></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>- once or twice daily: within 3 hour interval</td>
<td>5</td>
</tr>
<tr>
<td>- once daily: within 4 hour interval and twice daily: within 2 hour interval</td>
<td>1</td>
</tr>
<tr>
<td>- once or twice daily: no interval allowed</td>
<td>1</td>
</tr>
<tr>
<td>- twice daily: within 1 hour interval and thrice daily: within 1 hour interval</td>
<td>1</td>
</tr>
<tr>
<td>- twice daily: within 3 hour interval</td>
<td>1</td>
</tr>
<tr>
<td>- twice or thrice daily: within 1, 2, 3 hour interval</td>
<td>1</td>
</tr>
<tr>
<td>- no specified dosing: within 2 hour interval</td>
<td>2</td>
</tr>
<tr>
<td>- no specified dosing, no specified interval</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>- once daily: within 2 hour interval and twice daily: within 1 hour interval</td>
<td>1</td>
</tr>
<tr>
<td>- once daily: within 6 hour interval and twice daily: within 3 hour interval</td>
<td>4</td>
</tr>
<tr>
<td>- once daily: within 6 hour interval</td>
<td>1</td>
</tr>
<tr>
<td>- once daily, no specified interval</td>
<td>1</td>
</tr>
<tr>
<td>- no specified dosing, no specified interval</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
</tr>
</tbody>
</table>

Out of the 11 categories of adherence measures, the most commonly used adherence measure in MEMS literature was C1: the number of doses taken (n=52, 78.79%). Around one third of the studies (n=22, 32.31%) used the measure of C2.1: the number of days with correct doses; and C3: the number of doses taken on schedule. C3 was used with different definitions of acceptable dosing.
intervals. A fewer proportion of the studies, around one tenth (n=7, 10.77%) used C2.2: the number of days with correct dosing.

3.4.2. The main category of missed doses

Table 3.8: MEMS studies using C5, C6 and C7

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td>C5 Number of missed doses</td>
<td>1</td>
</tr>
<tr>
<td>C6 Number of missed doses within defined interval</td>
<td>-</td>
</tr>
<tr>
<td>C7 Number of missed doses in days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td>(Number of drug holidays)</td>
<td></td>
</tr>
<tr>
<td>C7.1 Number of days with missed doses</td>
<td>-</td>
</tr>
<tr>
<td>for 1 day</td>
<td></td>
</tr>
<tr>
<td>C7.2 Number of days with 1 missed doses</td>
<td>-</td>
</tr>
<tr>
<td>for twice daily dosing</td>
<td></td>
</tr>
<tr>
<td>C7.3 Number of days with missed doses</td>
<td>-</td>
</tr>
<tr>
<td>for 1 day</td>
<td></td>
</tr>
<tr>
<td>C7.4 Number of days with missed doses</td>
<td>1</td>
</tr>
<tr>
<td>for 1-2 days</td>
<td></td>
</tr>
<tr>
<td>C7.5 Number of days with missed doses</td>
<td>-</td>
</tr>
<tr>
<td>for 2 days</td>
<td></td>
</tr>
<tr>
<td>C7.6 Number of days with missed doses</td>
<td>2</td>
</tr>
<tr>
<td>for at least 2 days</td>
<td></td>
</tr>
<tr>
<td>C7.7 Number of days with missed doses</td>
<td>1</td>
</tr>
<tr>
<td>for 3 days</td>
<td></td>
</tr>
<tr>
<td>C7.8 Number of days with missed doses</td>
<td>1</td>
</tr>
<tr>
<td>for 7 days</td>
<td></td>
</tr>
<tr>
<td>C7.9 Longest number of days with missed doses</td>
<td>1</td>
</tr>
</tbody>
</table>

Overall, the main category of missed doses was not commonly used in MEMS studies with 1 to 2 studies (1.5% to 3.1%) using each category or sub-categories for C7.
3.4.3. The main category of extra doses taken

Table 3.9: MEMS studies using C8

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>C8 Number of days with extra doses taken</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

3.4.4. The main category of timing

Table 3.10: MEMS studies using C9

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>C9 Timing</td>
<td></td>
</tr>
<tr>
<td>C9.1 The duration of the longest intervals between doses</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td>C9.2 Mode of hour distributions</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>C9.3 Coefficient of variation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td>C9.4 The proportion of timing of doses taken within correct timing intervals</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td>C9.5 Sum of the interval of timing between doses divided by the number of MEMS openings</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Overall, one study (1.5%) used each sub-category of the timing measure.

3.4.5. The main category of the impact of drug taking on drug effects

Table 3.11: MEMS studies using C10

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>C10 The impact of drug taking on drug effects</td>
<td></td>
</tr>
<tr>
<td>C10.1 Therapeutic coverage</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
### Category Number of studies

<table>
<thead>
<tr>
<th>Category</th>
<th>HIV</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10.2 Uncovered time in 24 hours for once and twice daily dosing</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Around one tenth of the studies (n=6, 9.23%) used this measure of the impact of drug taking on drug effects.

#### 3.4.6. Other categories

**Table 3.12: MEMS studies using C11**

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>C11 Other categories</td>
<td>HIV</td>
</tr>
<tr>
<td>C11.1 Number of days with equal or greater than one dose being taken</td>
<td>1</td>
</tr>
<tr>
<td>C11.2 Number of doses taken divided by number of prescribed days</td>
<td>-</td>
</tr>
</tbody>
</table>

3.5. Discussion

This study has provided an overview of measures of adherence used in a subset of MEMS literature in HIV and hypertension therapeutic areas. The study has developed a set of categories into which reported adherence measures can be grouped. Adherence measures were also illustrated. The frequency of the use of various adherence measures was then explored.

The categorisation of reported adherence measures included (1) the main category of doses taken, (2) the main category of missed doses, (3) the main category of extra doses taken, (4) the main category of timing, (5) the main category of the impact of drug taking on drug effects and (6) other categories. To compare to the initial approach of measuring adherence by Vrijens et al. [181], their first three adherence measures were covered in the above main categories (with percentage of days with correct doses and percentage of doses taken being included in the main category of doses taken; and percentage of drug holidays
being included in the main category of missed doses). However, their latter three adherence measures (timing variability of doses taken, percentage of too short or too long dosing intervals and median and quartiles of dosing intervals) were not covered in the above main categories. Although the main category of timing was reported, timing measures were different from what Vrijens et al. proposed.

The results showed that the percentage of doses taken was the most commonly used adherence measure in recruited MEMS studies. Although MEMS type devices have been used in research into adherence to better understand adherence patterns, MEMS capabilities have not been fully utilised. It is important to note here that percentage of doses taken is a less informative measure. That is, it is equivalent to the measurement of pill counts. Several incorrect drug taking scenarios cannot be detected by percentage of doses taken. Such scenarios include patients who may take the number of doses correctly but at wrong intervals. An example is a twice daily dosing drug that is suggested to be taken at around 12 hours apart to allow drug effects to be attained throughout the day. The number of doses taken cannot provide the information, for instance, of when a patient takes two doses at one time. Another example is when one extra dose is taken then followed by a missed dose, or many extra doses taken and followed by drug holidays. Percentage of doses taken recorded by MEMS, may be however, potentially more reliable than pill counts reported by patients, as the latter could be easily censored by patients.

Although day level data can be obtained using the number of days with correct doses, this measure seems to share limitations with the number of doses taken. That is, on any day, the correct number of doses may be taken but whether the dosing interval is acceptable or not is unknown. The number of days with correct dosing takes both numbers of doses and when the dose is taken into account and hence it has an additional advantage.

The number of doses taken on schedule may be perceived as a precise measure. The results showed that an allowed dosing interval varied across studies. For illustration, if an acceptable interval is 25%, this means that an allowed dosing interval is 6 hours, 3 hours and 2 hours for once daily, twice daily
and thrice daily dosing, respectively. It is important to reiterate that timing variability should be considered when monitoring adherence since this provides better understanding of actual adherence behaviour and the impact of this on pharmacokinetic-pharmacodynamic (PKPD) responses. However, timing variability may not be a major barrier for patients to achieve their treatment target as long as they rarely miss taking doses. That is, the impact of missed doses may be stronger compared to that of timing variability. Findings to support this will be further discussed in more detail in Chapter 5. Generally speaking, for drugs whose responses are directly driven from plasma concentrations, timing errors on average may be allowed up to the number of hours of prescribed intervals.

For the main category of missed dose measure, the point to note is that, for C7, the definition of the consecutive days with missed doses was not consistent across studies. This was occasionally referred to as drug holidays and hence it should be taken into account when comparing results across studies. Generally in the literature, the consecutive days of missed doses may probably be perceived based on a once daily dosing. However, to be more specific, consecutive missed doses should be determined in addition to a variety of number of days with missed doses. To illustrate, for twice and thrice daily dosing drugs with immediate effects, the effect below therapeutic success would likely be observed within the duration of three consecutive missed doses; or one day of missed doses. Therefore, there is no definite rule about the consecutive number of missed doses or that of days with missed doses. This measure should be considered individually depending on each drug property and dosing regimen.

There was one study using the main category of extra doses taken. It is probably because the focus of adherence MEMS studies has been more towards under taking of doses compared to an excess of doses.

The main category of timing looked at the aspect of timing per se rather than the aspect of the number of doses, or the aspect of the number of doses with timing. One study used each sub-category. Further information provided from
Chapter 3: Measures of adherence in the Medication Event Monitoring System literature

The main category of the impact of drug taking on drug effects considered beyond the patterns of drug taking i.e. the duration that drugs exert therapeutic effects given doses taken. This measure of therapeutic coverage is of importance since it accounts for the ultimate outcome of interest. Further discussion about the link between the patterns of drug taking and drug effects will be presented in Chapter 5 and Chapter 6.

There are three implications from this study for future MEMS studies. Firstly, this study has demonstrated that available MEMS studies have used a number of adherence measures. Therefore, it is prudent that the comparison across available MEMS studies should be conducted using the same level of adherence measures to obtain better comparable results. Secondly, although there have been a number of adherence measures reported, it appeared that the overall picture of the three phases of adherence i.e. initiation, implementation and discontinuation were not commonly obtained by using some of the reported adherence measures. In particular for the implementation phase, the information on when random missed doses and drug holidays happened in conjunction with the frequency of these events was lacking. Hence, there should be a consensus for future MEMS studies that aggregate adherence measures should be used, which can provide the entire picture of adherence process. This will allow for the consistent reporting of informative adherence data. Thirdly, it seemed that much available MEMS data did not distinguish among these three phases of adherence. Therefore, future MEMS data obtained from aggregate adherence measures should be compared at the same phase of adherence. This will enable future research to study imperfect adherence due to the specific phase i.e. delayed initiation, suboptimal implementation, or early discontinuation.

Hence, it is proposed that in addition to the four adherence measures by Vrijens et al., percentage of days with correct dosing, number of random missed doses per month and number of drug holidays per 3 months should be used for future MEMS studies. Percentage of days with correct dosing can account for this measure was 1) the most common timing of doses taken, 2) the average of timing of doses taken and 3) the variability in timing of doses taken.
both percentage of too short or too long dosing intervals and a missed dose component. The timeframe of a missed dose component will allow us to understand both the frequency and occurrence of missed doses.

3.6. Conclusions

This study has categorised adherence measures reported in a subset of MEMS literature based on the relevance of adherence measures. The study has shown that adherence measures varied across MEMS studies. Despite the advanced function of MEMS to record adherence patterns, the most commonly used adherence measure was percentage of doses taken per day. Future MEMS studies should use standardised aggregate adherence measures to consistently report the entire temporal patterns of adherence arising from initiation, implementation and discontinuation.
Chapter 4: A Medication Event Monitoring System feasibility study in New Zealand
4.1. Context

The previous chapters have demonstrated the benefits of using Medication Event Monitoring System (MEMS) as a measurement of adherence. The benefits include a better understanding of: 1) actual medication taking behaviour in patients as well as 2) the association between temporal patterns of adherence and pharmacokinetic-pharmacodynamic (PKPD) responses. The first benefit will be further discussed in this chapter and the second benefit will be discussed in Chapter 5 and Chapter 6. Since temporal patterns of adherence data can only be provided by MEMS type devices, this highlights the importance of MEMS studies. To decrease potential barriers with conducting studies, feasibility studies should be considered beforehand.

Several MEMS feasibility studies have been conducted in the therapeutic area of HIV [210-213]. Another MEMS feasibility study was in a paediatric transplantation area [214]. Some conflicting findings have been reported. For example, the appearance of MEMS was perceived as having both advantages and disadvantages in HIV patients in that it may conceal or disclose their disease status [213]. MEMS feasibility studies including patient acceptability for other chronic diseases have not been conducted. In Australia, there has been research investigating the feasibility and patient acceptability of the use of an electronic monitoring device for asthma, but not MEMS devices for oral medications [215]. No MEMS studies have been undertaken in New Zealand.

With regards to patient medication taking behaviour, it has been proposed in the “rule of sixes” by Urquhart (1998) [55] that one in six patients has a unique pattern of adherence comprising 1) perfect adherence, 2) correct doses taken but with timing variability, 3) one random missed dose happening any time, 4) drug holidays happening three to four times per year, 5) one or more drug holidays happening per month and 6) imperfect adherence but giving an impression of perfect adherence. To date, limited attention has been paid to evaluate whether the proposed rule of sixes holds true.
4.2. **Aims**

There are two overall aims in this work, and each overall aim includes specific objectives. The first overall aim is:

(1) To investigate the feasibility of conducting the first MEMS study in New Zealand.

For this first aim, the specific objectives are grouped into three phases, namely identification of patients, recruitment, and retention and patient acceptability as follows:

**Identification of patients**

1) To determine an appropriate approach to identify potential patients to be recruited into an adherence study.

**Recruitment**

2) To determine the recruitment rate for a range of diseases which will guide decisions for a larger study. Recruitment rate determined in this study is based on the given setting examined.

3) To investigate reasons for patients choosing not to participate in this study to identify potential barriers for a larger study.

**Retention and patient acceptability**

4) To investigate patient acceptability of the use of MEMS to identify potential barriers for a larger study.

5) To investigate the dropout rate, based on returned MEMS, to guide decisions regarding recruitment numbers for a larger study.

The second overall aim is:

(2) To explore patterns of adherence given MEMS data arising from the feasibility study.

For this second aim, the specific objectives are as follows:

1) To compare adherence results reported between percentage of doses taken and percentage of days with correct dosing.

2) To evaluate the rule of sixes.

3) To determine patterns of adherence observed in this group of patients.
4.3. **Methods**

This work is divided into two parts relating to the overall aims.

4.3.1. **The feasibility of conducting the first MEMS study in New Zealand**

This study was conducted at a single community pharmacy in Dunedin, New Zealand from September to November 2012. The owner of the pharmacy was invited to be involved in the study and she agreed to assist after the researcher explained the study. The researcher provided the owner with a pharmacist information sheet with the key details of this study. The owner also informed pharmacists, staff and technicians at the pharmacy of this study, in order to get their assistance. General Practitioners (GPs) at an adjacent medical centre were informed of the proposed study, the use of MEMS and the potential involvement of their patients via a letter and GP information sheet. The study was approved by the Southern Health and Disability Ethics Committees (Ethic Committee Reference: 12/STH/7).

Methods are discussed below relating to each specific objective of identification of patients, recruitment, and retention and patient acceptability.

**Identification of patients**

The inclusion criteria for this feasibility study were broad and included all adult patients, defined as patients aged above 18 years old, with chronic diseases that were expected to have a minimum of 1 year treatment with a medication. Chronic diseases may include diabetes mellitus, hypertension, dyslipidaemia, gout, asthma, gastrointestinal disease. Although some patients may have multiple chronic diseases and require multiple medications, only one chronic disease and one medication for the treatment of this disease was studied per patient. The researcher provided pharmacists with the list of possible diseases. Pharmacists then chose the studied medication based on the provided list. Patients were excluded if they had cognitive impairment and/or were unable to provide written informed consent. Prior to initiation of recruitment, pharmacists identified areas for concerns. This included the type of medications to be
transferred into MEMS i.e. non-strip and blister packaging medications. These concerns were considered during the identification phase in addition to the inclusion and exclusion criteria identified by the research team.

Eligible patients were classified into three groups as follows:

1) Group 1 patients: patients who presented their prescriptions and waited for their medications.

2) Group 2 patients: patients who dropped their prescriptions off to the pharmacy and returned later to collect their medications at their convenience, which may not be on the same day.

3) Group 3 patients: patients who would need to return to the pharmacy to extend or refill medication supply identified by pharmacists.

**Recruitment**

The aim was to include 30 patients during the initial recruitment phase. The maximum period of the recruitment phase was set as two months. Pharmacists scanned through patient prescriptions when performing medication clinical checks or when entering patient medication information into their history on the pharmacy system. For group 3 patients, pharmacists scanned through their history on the pharmacy system. If one of their medications matched the suitable diseases, they were invited to participate in this study.

Patients were invited to participate through the following approaches:

1) For group 1 patients or group 2 patients who could spare some time, pharmacists or staff introduced the researcher to patients. The researcher started initial conversation with patients. They were briefly informed of the background of the study and patient involvement regarding the change of a regular bottle to a MEMS.

2) For group 2 patients, stickers indicating “see … (the researcher’s name) for the study” were labelled on medication packages prepared for them. The researcher was informed by pharmacists or staff when the patients turned up. When feasible, pharmacists or staff introduced the researcher to patients. The researcher then started the initial conversation with patients.
3) For group 3 patients, pharmacists contacted them by phone. Pharmacists started the initial conversation with patients. Dates that patients would go to the pharmacy to refill their prescriptions were noted for the researcher.

For patients who were willing to participate, they were recruited consecutively. For the first 15 patients, they were recruited based on the above inclusion criteria. For the second 15 patients, the inclusion criteria were tightened to focus on drugs of interest to the research team. This can be broken down into 3 groups: 1) statin medications (n=5), 2) diabetes medications (n=5) and 3) non-specified medication cases (n=5). The first reading of the MEMS bottle, which occurred during medication dispensing, was noted and discarded for all patients.

A more detailed explanation was conducted in a counselling room. The researcher went through a participant information sheet with patients. Patients were informed that one of their medications would be dispensed into a MEMS instead of their regular tablet bottle. They were then instructed on the appropriate use of the device, that they should take their medications as they normally would and that no data captured would be linked back to them or shared with the pharmacist or doctor. A sample MEMS bottle was shown to them. Patients were encouraged to ask any questions regarding the appropriate use of MEMS as well as given recommendations about what they should do. The recommendations included:

- To bring a MEMS along with them while travelling.
- To leave all pills in a MEMS, not to transfer their medications into adherence aids or other containers.
- To keep a MEMS away from small children in their family who may play with it.

Patients were also given a numbered courier bag to return a MEMS to the research team when the medication supply had run out (mostly, in either one or three months depending on medication and the period of supply determined by the prescriber). Patients were told to finish their remaining medications if there were still any left from the previous dispensing and were asked about the
approximate start time of the current medications dispensed in MEMS. The researcher accordingly estimated the approximate returning time and ensured that patients were aware of this. They were also advised of an enclosed questionnaire for their comments on the acceptability of the use of MEMS; and to return it along with their MEMS. As part of the consent process, patients then signed a consent form with details of the research project. Patients were also asked for their address and contact number, and given contact details for the research team. Whether patients found this study acceptable, the use of MEMS and patients’ comments were also noted during this conversation. Patients were given a copy of both the participant information sheet and consent form to keep (see Appendix A.2.1 for an example of the participant information sheet and consent form).

Medication dispensing was still conducted by pharmacists. For group 2 patients, medications, which had already been dispensed into a regular bottle to avoid waiting time, were repackaged into a MEMS by pharmacists. When expected patients did not turn up, then MEMS codes were allocated consecutively. Patients were presented with their MEMS bottles by the researcher where possible.

For those who chose not to participate, the researcher noted their reason for this as per a developed list of potential reasons:

The reasons were:

- Not interested in the study
- Don’t want to change habits
- Don’t want to cope with new technology
- Don’t want medication taking behaviour to be observed
- Currently using medication taking aids
- Usually take medications out and place where easily noticeable
- Other (please identify)
Retention and patient acceptability

A questionnaire on how acceptable patients found the use of MEMS was enclosed in a courier bag. Patients were asked to return the questionnaire along with their MEMS in the provided courier bag. The questionnaire included a question asking whether patients would be willing to use MEMS for another prescription refill. If patients decided to discontinue using MEMS, they would be asked for their reasons for this.

The returned MEMS rate was recorded. If the devices were damaged or lost, this would also be recorded to identify how this occurred and thoughts about how this could be minimised.

The questionnaire for patient acceptability of the use of MEMS is presented here.
The acceptability of the use of the medication event monitoring system (MEMS) bottles

Name (please print)..................................................................................................................

Thank you for your time in completing this questionnaire. We are grateful for your contribution.

The questionnaire should take you less than five minutes to complete.

Should you require any clarification on any of the questions, please contact:

Dr Rhiannon Braund rhiannon.braund@otago.ac.nz 03 479 7240
Miss Piyanan Assawasuwannakit piyanan.assawasuwannakit@otago.ac.nz 03 479 7321

Please return this questionnaire along with your MEMS bottle in the courier bag provided.

Thank you for your cooperation
• How easy was it to use the medication event monitoring system (MEMS) bottle?
  □ very easy ☐ easy ☐ neutral ☐ difficult ☐ very difficult
Any comments?

• How practical was it to use the MEMS bottle?
  □ very practical ☐ practical ☐ neutral ☐ impractical ☐ very impractical
Any comments?

• Were you comfortable with using the MEMS bottle?
  □ very comfortable ☐ comfortable ☐ neutral ☐ uncomfortable ☐ very uncomfortable
Any comments?

• Do you think the MEMS bottle might have affected your medication taking behaviour?
  □ Yes,
  because.............................................................................................................................
  □ No,
  because.............................................................................................................................

• Did you have any problems with using the MEMS bottle?
.............................................................................................................................
.............................................................................................................................

• Would you be willing to use the MEMS bottle for another prescription refill?
  □ Yes
  □ No,
  because.............................................................................................................................

• Any other comments?
.............................................................................................................................
.............................................................................................................................
4.3.2. Patterns of adherence from MEMS data arising from the feasibility study

For all returned MEMS bottles, each patient’s MEMS data were transferred via a MEMS reader to a computer. Each patient adherence profile was then summarised using some adherence measures proposed by Vrijens et al. [181] mentioned in Chapter 3, namely 1) percentage of doses taken, 2) percentage of days with correct doses, 3) percentage of drug holidays, and 4) percentage of too short or too long dosing intervals.

Drug holidays here, for both once and twice daily dosing, are considered as three or more consecutive missed doses but not more than six consecutive missed doses.

Here, percentage of too short or too long dosing intervals was determined based on the following approaches:

- Each patient’s mode of timing of doses taken over the monitoring period was first determined. For patients prescribed with twice daily dosing, the mode of timing of doses taken comprised that of morning as well as evening doses.
  - A correct dosing interval was then defined as:
    - an interval of 6 hours sooner or later than the mode of timing of doses taken for once daily dosing i.e. mode of timing ± 6 hours.
    - an interval of 3 hours sooner or later than the mode of timing of doses taken, for morning doses and evening doses, for twice daily dosing i.e. morning mode of timing ± 3 hours and evening mode of timing ± 3 hours.
  - Hence, too short dosing intervals was defined as dosing intervals occurring before (mode of timing – 6 hours) for once daily dosing. The same criterion applied to twice daily dosing.
  - Hence, too long dosing intervals was defined as dosing intervals occurring after (mode of timing + 6 hours) for once daily dosing. The same criterion applied to twice daily dosing.

Subsequently, based on aggregate adherence measures that were proposed in Chapter 3, all the adherence profiles were also summarised using percentage of days with correct dosing as well as percentage of random missed doses per
month. Here, percentage of days with correct dosing is defined as percentage of days with both correct number of doses taken and correct timing. Correct timing has been previously described as: 1) an interval of 6 hours sooner or later than the mode of timing of doses taken for once daily dosing and 2) for twice daily dosing, an interval of 3 hours sooner or later than the mode of timing of doses taken, for morning doses and evening doses.

The difference of adherence results reported, when calculated by a global measure in comparison to a more appropriate measure, was demonstrated. For illustration, percentage of doses taken and percentage of days with correct dosing were respectively chosen as a global and a more appropriate measure.

The rule of sixes was evaluated using these summarised MEMS adherence data. Given that the data may not follow the rule of sixes, patterns of adherence observed in this group of patients were then determined.

### 4.4. Results

#### 4.4.1. The feasibility of conducting the first MEMS study in New Zealand

**Identification of patients**

Pharmacists had concerns which may limit the characteristics of potential patients based on prescribed medications, and these concerns are discussed here.

- **Blister packaging medications:** Only non-strip packaging medications were accepted by pharmacists since they were concerned that patients may miss some information on the label of blister packaging medications.
- **“High risk” medications:** Pharmacists did not want warfarin prescriptions to be considered in this study since they perceived warfarin as a high risk drug.
- **Size of pills:** Pharmacists also pointed out that the size of a few drugs such as metformin could be relatively large and may not fit into MEMS. Hence, the researcher counted the number of metformin pills that could be transferred into MEMS. It was found that the prescription of thrice daily metformin 500 mg for a three-month supply i.e. 270 pills was
feasible to be one of the selected medications. However, if patients were prescribed with more than one tablet per dosing or with metformin 850 mg then the capacity of MEMS may not be sufficient.

- Medications that required desiccants could not be a candidate.
- Medications that were prescribed for different doses for alternate days:
  Due to the complexity of the regimen, pharmacists suggested excluding this scenario.

**Recruitment**

Overall, in order to recruit the target of 30 patients, 41 patients were approached. Of the recruited patients, 19 were male and 11 were female. The mean age was 60 years (IQR 49-67.75 years). Twenty eight patients identified their ethnicity as New Zealander, 1 as European and 1 as English. In total, it took 12 days to recruit 30 patients with 3 days to recruit the first 15 patients. For both statin and diabetes medication cases, it took 4 different days to recruit 5 patients for each case. For another 5 non-specified medication cases, it took another 3 days to recruit these.

Because the researcher did not have access to information on patient disease, recruited patients were only categorised by the type of medications, as shown in Table 4.1.
Table 4.1: The number of patients recruited categorised by the type of medications

<table>
<thead>
<tr>
<th>Type of medications</th>
<th>Number of patients recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>omeprazole</td>
<td>6</td>
</tr>
<tr>
<td>cilazapril</td>
<td>5</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>5</td>
</tr>
<tr>
<td>metformin</td>
<td>4</td>
</tr>
<tr>
<td>allopurinol</td>
<td>2</td>
</tr>
<tr>
<td>candesartan</td>
<td>2</td>
</tr>
<tr>
<td>bendrofluazide</td>
<td>1</td>
</tr>
<tr>
<td>doxycycline</td>
<td>1</td>
</tr>
<tr>
<td>eltroxin</td>
<td>1</td>
</tr>
<tr>
<td>gliclazide</td>
<td>1</td>
</tr>
<tr>
<td>lithium carbonate</td>
<td>1</td>
</tr>
<tr>
<td>ranitidine</td>
<td>1</td>
</tr>
</tbody>
</table>

Eleven patients declined to participate. The reasons for not participating are shown in Table 4.2.

Table 4.2: Patients’ reasons for declining to participate in this study

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently using medication taking aids e.g. medication trays</td>
<td>5</td>
</tr>
<tr>
<td>Not interested in the study</td>
<td>3</td>
</tr>
<tr>
<td>Usually take medications out and place where easily noticeable</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>- Three month period of using MEMS was too long.</td>
<td>1</td>
</tr>
<tr>
<td>- Usually take sufficient medications out of bottle while away.</td>
<td>1</td>
</tr>
</tbody>
</table>
Retention and patient acceptability

Of the 30 recruited patients, 1 patient prescribed with metformin passed away. Of the remaining 29 MEMS bottles, 25 bottles were returned to the research team. This gives the retention rate of 86.21%. There were no damaged bottles. Table 4.3 shows the number of MEMS returned categorised by the type of medications.

**Table 4.3: The number of MEMS returned categorised by the type of medications**

<table>
<thead>
<tr>
<th>Type of medications</th>
<th>Number of MEMS returned</th>
</tr>
</thead>
<tbody>
<tr>
<td>omeprazole</td>
<td>5</td>
</tr>
<tr>
<td>cilazapril</td>
<td>5</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>3</td>
</tr>
<tr>
<td>metformin</td>
<td>2</td>
</tr>
<tr>
<td>allopurinol</td>
<td>2</td>
</tr>
<tr>
<td>candesartan</td>
<td>2</td>
</tr>
<tr>
<td>bendrofluazide</td>
<td>1</td>
</tr>
<tr>
<td>doxycycline</td>
<td>1</td>
</tr>
<tr>
<td>eltroxin</td>
<td>1</td>
</tr>
<tr>
<td>gliclazide</td>
<td>1</td>
</tr>
<tr>
<td>lithium carbonate</td>
<td>1</td>
</tr>
<tr>
<td>ranitidine</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
</tr>
</tbody>
</table>

With regards to the acceptability of the use of MEMS, Figures 4.1, 4.2 and 4.3 show the number of patients reporting on the ease, practicality and comfort of using MEMS. Further comments by patients for each question are presented in Tables 4.4, 4.5 and 4.6. Details for the questions on whether or not MEMS might have affected patient medication taking behaviour; did patients have any problems with using MEMS; and would patients be willing to use MEMS for another prescription are presented in Tables 4.7, 4.8 and 4.9, respectively. Table 4.10 presents other comments that patients may have.
Chapter 4: A Medication Event Monitoring System feasibility study in New Zealand

Figure 4.1: Number of patients reporting on the ease of using MEMS

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very easy</td>
<td>14</td>
<td>56%</td>
</tr>
<tr>
<td>Easy</td>
<td>9</td>
<td>36%</td>
</tr>
<tr>
<td>Neutral</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>Difficult</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Very difficult</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 4.2: Number of patients reporting on the practicality of using MEMS

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very practical</td>
<td>8</td>
<td>32%</td>
</tr>
<tr>
<td>Practical</td>
<td>11</td>
<td>44%</td>
</tr>
<tr>
<td>Neutral</td>
<td>6</td>
<td>24%</td>
</tr>
<tr>
<td>Impractical</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Very impractical</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 4.3: Number of patients reporting on the comfort of using MEMS

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very comfortable</td>
<td>12</td>
<td>48%</td>
</tr>
<tr>
<td>Comfortable</td>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>Neutral</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>Uncomfortable</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Very uncomfortable</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
Table 4.4: Details for the question: how easy was it to use the MEMS bottle?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Details</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(number of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. How easy was it to use the MEMS bottle?</td>
<td>Very easy (14)</td>
<td>- The relatively large size of MEMS reminded patients to take medications.</td>
<td>- The size of MEMS was large for travelling.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- A MEMS was simply another type of medication bottle which did not affect patients’ routine of taking medications</td>
<td>- The appearance of MEMS was not nice which could be seen by others when travelling.</td>
</tr>
<tr>
<td></td>
<td>Easy (9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Neutral (2)</td>
<td>-</td>
<td>- MEMS caps were not designed for pills to be poured onto the inside of the cap.</td>
</tr>
<tr>
<td></td>
<td>Difficult (-)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Very difficult (-)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Table 4.5: Details for the question: how practical was it to use the MEMS bottle?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Details</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. How practical was it to use the MEMS bottle?</td>
<td>Very practical (8)</td>
<td>- The very large size of MEMS was very practical.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Practical (11)</td>
<td>- A MEMS was simply another type of medication bottle that could be placed beside the bed for medications being taken in the morning.</td>
<td>- The size of MEMS was large for travelling; however this did not prevent patients from bringing MEMS along.</td>
</tr>
<tr>
<td></td>
<td>Neutral (6)</td>
<td>- The size of MEMS could have been smaller to suit small pills.</td>
<td>- The size of MEMS was large for travelling.</td>
</tr>
<tr>
<td></td>
<td>Impractical (-)</td>
<td>- MEMS caps were not designed for pills to be poured onto the inside of the cap. Therefore, extracting pills using fingers from inside the bottle was not practical.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Very impractical (-)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4.6: Details for the question: were you comfortable with using the MEMS bottle?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Details</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Were you comfortable with using the MEMS bottle?</td>
<td>Very comfortable (12)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Comfortable (10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Neutral (2)</td>
<td>-</td>
<td>- MEMS caps were not designed for pills to be poured onto the inside of the cap. Therefore, pills may fall out as a result.</td>
</tr>
<tr>
<td></td>
<td>Uncomfortable (1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Very uncomfortable (-)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4.7: Details for the question: do you think the MEMS bottle might have affected your medication taking behaviour?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Do you think the MEMS bottle might have affected your medication</td>
<td>Yes (6)</td>
<td>- The awareness of medication taking behaviour being monitored made patients more adherent.</td>
</tr>
<tr>
<td>taking behaviour?</td>
<td></td>
<td>- The unique characteristics of MEMS reminded patients to take medications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medications dispensed into MEMS were scheduled at a different dosing which reminded patients to take medications.</td>
</tr>
<tr>
<td></td>
<td>No (19)</td>
<td>- Taking medication was a part of daily routine irrespective of using MEMS or regular bottles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MEMS bottles were perceived as regular bottles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MEMS bottles were used as per instructions given by the researcher.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medications dispensed into MEMS were taken concurrently with other medications dispensed into regular bottles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medications dispensed into MEMS were taken concurrently with other medications dispensed weekly into medication aids.</td>
</tr>
</tbody>
</table>

76% of patients (n=19) reported that MEMS did not affect their medication taking behaviour.
**Table 4.8: Details for the question: did you have any problems with using MEMS?**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Did you have any problems with using MEMS?</td>
<td>No (20)</td>
<td>- The size of MEMS was large for travelling.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The size of MEMS was large; however it may be good for older people with pain in their fingers/hand.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The bottle was not designed for pills to be extracted by pouring onto the inside of the cap.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Medications could not be taken out of MEMS beforehand.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- A MEMS needed to be kept away from children to prevent them from opening it.</td>
</tr>
</tbody>
</table>

76% of patients (n=20) reported that there was no problem with using MEMS.
### Table 4.9: Details for the question: would you be willing to use the MEMS bottle for another prescription?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Would you be willing to use the MEMS bottle for another prescription?</td>
<td>Yes (18)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>No (7)</td>
<td>- The size of MEMS was large.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Long travelling would not allow using MEMS appropriately.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Regular bottles were fine with patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Using MEMS was new to regular habits of medication taking that had been formed over many years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Using MEMS for one prescription was enough for patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No reasons provided.</td>
</tr>
</tbody>
</table>

80% of patients (n=18) reported that they would be willing to use MEMS for another prescription.
### Table 4.10: Details for the question: other comments?

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Other comments?</td>
<td>- Being informed of actual medication taking behaviour may benefit patients.</td>
</tr>
<tr>
<td></td>
<td>- The dates when medications were not taken from MEMS due to a minor surgery and the restriction of taking medications were noted.</td>
</tr>
<tr>
<td></td>
<td>- MEMS had to be taken along on vacation although another medication supply was available as usual.</td>
</tr>
<tr>
<td></td>
<td>- Patients noted the start and stop dates of using MEMS over three months to inform the researcher.</td>
</tr>
<tr>
<td></td>
<td>- Patients also noted dates and times of unintentional openings of MEMS and missed doses to inform the researcher.</td>
</tr>
<tr>
<td></td>
<td>- The issue of different time zones in different countries and hence MEMS profiles needing to be adjusted was noted.</td>
</tr>
<tr>
<td></td>
<td>- The concern about whether MEMS could be X-rayed at the airport was raised.</td>
</tr>
</tbody>
</table>
4.4.2. Patterns of adherence from MEMS data arising from the feasibility study

Table 4.11 displays the results of adherence of each patient (n=25) along with their MEMS monitoring period as well as drug and dosing prescribed. The number of random missed doses is presented as the total number over the monitoring period and the number occurring per month.

**Table 4.11: Results of adherence of each patient (n=25)**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Drug and dosing prescribed</th>
<th>MEMS monitoring period (days)</th>
<th>1) Percentage of doses taken</th>
<th>2) Percentage of days with correct doses</th>
<th>3) Number of drug holidays</th>
<th>4) Percentage of too short or too long dosing intervals</th>
<th>5) Percentage of days with correct dosing</th>
<th>6) Number of random missed doses</th>
<th>1st month*</th>
<th>2nd month*</th>
<th>3rd month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>omeprazole 20 mg OD</td>
<td>62</td>
<td>96.8</td>
<td>96.8</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>96.8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>omeprazole 20 mg OD</td>
<td>91</td>
<td>63.7</td>
<td>61.5</td>
<td>3</td>
<td>too short: 0 too long: 4</td>
<td>59.3</td>
<td>25</td>
<td>6</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>omeprazole 20 mg OD</td>
<td>90</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>100</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>omeprazole 40 mg OD</td>
<td>91</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>100</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>omeprazole 20 mg OD</td>
<td>101</td>
<td>93.1</td>
<td>87.1</td>
<td>0</td>
<td>too short: 2 too long: 1</td>
<td>86.1</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Drug and dosing prescribed</td>
<td>MEMS monitoring period (days)</td>
<td>1) Percentage of doses taken</td>
<td>2) Percentage of days with correct doses</td>
<td>3) Number of drug holidays</td>
<td>4) Percentage of too short or too long dosing intervals</td>
<td>5) Percentage of days with correct dosing</td>
<td>6) Number of random missed doses</td>
<td>1st month*</td>
<td>2nd month*</td>
<td>3rd month*</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------</td>
<td>------------------------------</td>
<td>------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>1</td>
<td>cilazapril 5 mg OD</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>98</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>cilazapril 500 mcg OD</td>
<td>93</td>
<td>95.7</td>
<td>93.5</td>
<td>0</td>
<td>too short: 2 too long: 0</td>
<td>92.5</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>cilazapril 500 mcg OD</td>
<td>100</td>
<td>87</td>
<td>87</td>
<td>1</td>
<td>too short: 0 too long: 7</td>
<td>80</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>cilazapril 2.5 mg OD</td>
<td>65</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>100</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>cilazapril 2.5 mg OD</td>
<td>88</td>
<td>100</td>
<td>95.5</td>
<td>0</td>
<td>too short: 8 too long: 3</td>
<td>86.4</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>atorvastatin 20 mg OD</td>
<td>103</td>
<td>88.3</td>
<td>82.5</td>
<td>1</td>
<td>too short: 0 too long: 3</td>
<td>82.5</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>atorvastatin 80 mg OD</td>
<td>95</td>
<td>95.8</td>
<td>95.8</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>95.8</td>
<td>4</td>
<td>-</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>atorvastatin 10 mg OD</td>
<td>91</td>
<td>100</td>
<td>95.6</td>
<td>0</td>
<td>too short: 0 too long: 1</td>
<td>95.6</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Drug and dosing prescribed</td>
<td>MEMS monitoring period (days)</td>
<td>1) Percentage of doses taken</td>
<td>2) Percentage of days with correct doses</td>
<td>3) Number of drug holidays</td>
<td>4) Percentage of too short or too long dosing intervals</td>
<td>5) Percentage of days with correct dosing</td>
<td>6) Number of random missed doses</td>
<td>1st month*</td>
<td>2nd month*</td>
<td>3rd month*</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------</td>
<td>------------------------------</td>
<td>-----------------------------</td>
<td>------------------------------------------</td>
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<td>----------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>22</td>
<td>metformin 500 mg BID</td>
<td>109</td>
<td>81.2</td>
<td>64.2</td>
<td>0</td>
<td>- morning too short: 0 too long: 3 - evening too short: 4 too long: 0</td>
<td>56.9</td>
<td>41</td>
<td>14</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>25</td>
<td>metformin 500 mg BID</td>
<td>93</td>
<td>96.2</td>
<td>88.2</td>
<td>0</td>
<td>- morning too short: 0 too long: 2 - evening too short: 0 too long: 1</td>
<td>87.1</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>allopurinol 300 mg OD</td>
<td>90</td>
<td>98.9</td>
<td>98.9</td>
<td>0</td>
<td>too short: 0 too long: 1</td>
<td>97.8</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>allopurinol 300 mg OD</td>
<td>90</td>
<td>98.9</td>
<td>98.9</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>98.9</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>candesartan 16 mg OD</td>
<td>92</td>
<td>97.8</td>
<td>97.8</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>97.8</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>candesartan 16 mg OD</td>
<td>93</td>
<td>96.8</td>
<td>96.8</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>96.8</td>
<td>3</td>
<td>-</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
### Chapter 4: A Medication Event Monitoring System feasibility study in New Zealand

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Drug and dosing prescribed</th>
<th>MEMS monitoring period (days)</th>
<th>1) Percentage of doses taken</th>
<th>2) Percentage of days with correct doses</th>
<th>3) Number of drug holidays</th>
<th>4) Percentage of too short or too long dosing intervals</th>
<th>5) Percentage of days with correct dosing</th>
<th>6) Number of random missed doses</th>
<th>1st month*</th>
<th>2nd month*</th>
<th>3rd month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>bendrofluazide 2.5 mg OD</td>
<td>92</td>
<td>97.8</td>
<td>95.7</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>95.7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>doxycycline 100 mg OD</td>
<td>90</td>
<td>100</td>
<td>93.3</td>
<td>1</td>
<td>too short: 1 too long: 0</td>
<td>93.3</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>eltroxin 100 mcg OD</td>
<td>84</td>
<td>81</td>
<td>76.2</td>
<td>1</td>
<td>too short: 11 too long: 18</td>
<td>54.8</td>
<td>15</td>
<td>3</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>gliclazide 80 mg BID</td>
<td>91</td>
<td>98.9</td>
<td>95.6</td>
<td>0</td>
<td>- morning too short: 3 too long: 0</td>
<td>93.4</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>lithium carbonate 250 mg BID</td>
<td>31</td>
<td>87.1</td>
<td>83.9</td>
<td>2</td>
<td>- morning too short: 0 too long: 8</td>
<td>71</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>ranitidine 300 mg OD</td>
<td>91</td>
<td>101.1+</td>
<td>98.9</td>
<td>0</td>
<td>too short: 0 too long: 0</td>
<td>98.9</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
OD is once daily dosing. BID is twice daily dosing.

* Number of random missed doses occurring per month: 1st month, 2nd month and 3rd month.

* This patient took one extra dose on one day.

The data describe the implementation phase. In addition, note that as per the observed treatment period, there were no patients with late initiation or early discontinuation.
The difference of adherence results of each patient, when measuring by percentage of doses taken and percentage of days with correct dosing, is displayed in Table 4.12.

**Table 4.12: The difference of adherence percentage measured by percentage of doses taken and percentage of days with correct dosing**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Percentage of doses taken</th>
<th>Percentage of days with correct dosing</th>
<th>The difference of the two percentage values</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>101.1</td>
<td>98.9</td>
<td>2.2</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>93.3</td>
<td>6.7</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>86.4</td>
<td>13.6</td>
</tr>
<tr>
<td>23</td>
<td>100</td>
<td>95.6</td>
<td>4.4</td>
</tr>
<tr>
<td>16</td>
<td>98.9</td>
<td>97.8</td>
<td>1.1</td>
</tr>
<tr>
<td>18</td>
<td>98.9</td>
<td>98.9</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>98.9</td>
<td>93.4</td>
<td>5.5</td>
</tr>
<tr>
<td>1</td>
<td>98</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>97.8</td>
<td>97.8</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>97.8</td>
<td>95.7</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>96.8</td>
<td>96.8</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>96.8</td>
<td>96.8</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>96.2</td>
<td>87.1</td>
<td>9.1</td>
</tr>
<tr>
<td>19</td>
<td>95.8</td>
<td>95.8</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>95.7</td>
<td>92.5</td>
<td>3.2</td>
</tr>
</tbody>
</table>
The results show that percentage of doses taken gave either the same or the higher value compared to percentage of days with correct dosing. Overall, a mean ± SD of the difference of the two percentage values was 5.5±7.4% in this group of patients. It can be seen that the difference of the two percentage values varied among patients. In some patients, such as patients 11, 15 and 22, the two values were markedly different indicating that solely using percentage of doses taken to measure adherence was not appropriate. To exemplify this, for patient 15, it appeared this patient was perfectly adherent with percentage of doses taken (100%) but not so adherent with percentage of days with correct dosing (86.4%).

Evaluation of the rule of sixes using the adherence data summarised in Table 4.11 is presented in Table 4.13.
Table 4.13: Evaluation of the rule of sixes based on observed adherence data in this MEMS feasibility study

<table>
<thead>
<tr>
<th>Description of each rule of sixes</th>
<th>Observations of each rule from this group of patients (the number of observations/ the total number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>takes all doses exactly as prescribed</td>
<td>0/25</td>
</tr>
<tr>
<td>takes all prescribed doses but timing is fairly inconsistent</td>
<td>3/25</td>
</tr>
<tr>
<td>misses one occasional dose on any days</td>
<td>2/25</td>
</tr>
<tr>
<td>has a drug holiday three to four times per year</td>
<td>cannot be tested in this study</td>
</tr>
<tr>
<td>has a drug holiday or more than one per month</td>
<td>2/25</td>
</tr>
<tr>
<td>takes few doses or none but creates the impression of good adherence</td>
<td>cannot be tested</td>
</tr>
</tbody>
</table>

Since the results showed that medication taking behaviour in this group of patients did not follow the rule of sixes, patterns of adherence observed in this group of patients are reported as shown in Table 4.14.

Table 4.14: patterns of adherence observed in this group of patients

<table>
<thead>
<tr>
<th>Description of each pattern of adherence</th>
<th>Observations of each pattern of adherence (the number of observations/ the total number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>takes all prescribed doses but timing is fairly inconsistent</td>
<td>3/25</td>
</tr>
<tr>
<td>has 90% to less than 100% of days with correct dosing</td>
<td>13/25</td>
</tr>
<tr>
<td>has 80% to 90% of days with correct dosing</td>
<td>5/25</td>
</tr>
<tr>
<td>has 55% to 75% of days with correct dosing</td>
<td>4/25</td>
</tr>
<tr>
<td>has 1 to 5 random missed doses for 1st, 2nd and 3rd month</td>
<td>5/22⁺</td>
</tr>
<tr>
<td>has 1 drug holiday per 3 months</td>
<td>4/22⁺</td>
</tr>
</tbody>
</table>
Patients prescribed with a monitoring period less than 3 months were excluded.

4.5. Discussion

This study has investigated the feasibility of conducting the first MEMS study in New Zealand to identify potential barriers when further conducting a further, larger study. The potential barriers were associated with three phases, namely identification of patients, recruitment, and retention and patient acceptability. Another part of this study has looked at adherence data obtained from the MEMS feasibility study. The adherence data were summarised using adherence measures suggested in Chapter 3. Percentage of doses taken per day and percentage of days with correct dosing, were then compared to demonstrate the inappropriateness of using the former criterion. Subsequently, the rule of sixes was evaluated based on this set of adherence results. Given that medication taking behaviour in this group of patients did not follow the rule of sixes, patterns of adherence observed here were reported.

The discussion is divided into two parts:

4.5.1. The feasibility of conducting the first MEMS study in New Zealand

There were some concerns noted for identification of patients. These included the exclusion of blister packaging medications and prescriptions perceived by pharmacists as “high-risk”, suggesting that future MEMS studies should take these issues into account prior to designing the study.

For the recruitment process, several studies have supported the notion that it was feasible to recruit patients through a community pharmacy [216-220]. This work found that the recruitment rate appeared higher when diseases studied were not specified, as it took 3 days to recruit the first 15 patients. However, this recruitment rate may not be consistent since it took 3 days to recruit another 5 patients with non-specified medications in the second 15 patients. When recruiting patients based on specified diseases of interest, the recruitment rate was lower. In this study it was found that it took 4 days to recruit 5 patients
prescribed statins as well as diabetes medications. Based on these findings, it may take around 1 day to recruit 1 patient with a specified medication of interest. Supposing there were 60 patients per arm in a larger study, this may take around 2-4 months to recruit patients per arm. To obtain a higher rate of recruitment in a larger study, it is recommended that an approach where pharmacists scan patient history of medication refills on a pharmacy database may be highly effective. It seems likely that potential patients could be mostly included, which may not be feasible when researchers are waiting for patients to turn up. This approach also allows timeframes of the year to be identified when most potential patients require their prescription refills, as most timeframes are either one or three month supply. Given that patients have already built a rapport with pharmacists, this may facilitate higher chances of recruitment as well.

The main reason for patients choosing not to participate in this study was that they had been using adherence aids such as medication trays. This finding corresponds to previous studies regarding patients using pill boxes [210, 211]. The second most reported reason was that patients were not interested in the study. This issue of patient preference of adherence aids over MEMS may not be easily overcome given that MEMS are not designed for poly-medications. Hence for a larger study, the timeframe for recruitment should consider this barrier. As an example, this study aimed to recruit 30 patients but there were 11 patients who declined to participate, which was around one third of the expected number of patients. It could be the case that patients who declined to participate in this study may have different characteristics e.g. sex, age compared to those who participated. However, there was no information obtained for patients who declined to participate.

Discussion with respect to patient acceptability of the use MEMS is as follows:

- For the ease of using MEMS, almost all patients reported that it was easy/very easy with around half of patients reporting that it was very easy. Among the latter, although they perceived the use of MEMS as very easy, some comments were further noted as barriers. These were mainly related to using
MEMS when travelling due to the size and appearance of MEMS. However, a positive comment on the large size of MEMS was that it reminded patients to take medications. The MEMS bulkiness was also raised here [214]. The study of Lyimo *et al.* [213] also found that patients in general commented that the use of MEMS was “simple and acceptable”. The findings regarding the barrier of MEMS when travelling is not surprising. This has been noted as one of the most commonly encountered problems in previous studies [210, 211, 213, 221] which resulted in patients leaving MEMS at home to avoid losing it [213], patients suspending taking pills from MEMS but taking from supply at another place [210] and patients taking extra pills from MEMS [211, 221]. However, in this study, it seemed that although patients faced difficulties with bringing MEMS along while travelling, they still used MEMS appropriately. This assumption was made based on patient comments: medications could not be taken out of MEMS beforehand; long travelling would not allow using MEMS appropriately; and they needed to remember to take MEMS along on vacation although another medication supply was available as usual.

- For the practicality of the use of MEMS, around three quarters of patients reported that it was practical/very practical with a similar proportion of patients reporting that it was practical or very practical. Details given were related to the large size of MEMS which seemed not to negatively affect the use of MEMS. The large size of MEMS was seen as a barrier among those who found its practicality to be neutral.

- Almost all patients reported that the use of MEMS was comfortable/very comfortable with a similar proportion of patients reporting that it was comfortable or very comfortable. No further details were given for these.

- Whether or not MEMS might have affected patients’ medication taking behaviour, three quarters of patients reported that the use of MEMS did not affect their medication taking behaviour. One of the reasons that MEMS affected medication taking behaviour was that patients were aware of being monitored, which in turn leads to being more adherent. This finding is consistent with
previous studies [210, 211, 213, 214] with one study finding that MEMS resulted in both increased and decreased adherence [210].

- Twenty percent of patients reported problems with using MEMS. Issues apart from the size of MEMS included that pills need to be taken from the bottle at the time of taking medications which may not be convenient for certain situations, and the need to keep the bottle away from children.

- Twenty eight percent of patients would not be willing to use MEMS for another prescription. Reasons for this included using regular bottles with regular habits seemed fine with patients.

In this study, the retention rate of returned MEMS was 86% which is relatively higher than that of the study of Konkle-Parker et al. (58%) [212]. It is suggested that a larger study should consider a further 20% recruitment of patients to compensate for possible dropouts. With respect to the characteristics of patients who did not return the MEMS bottles (n=4), of these, 75% were male. For comparison, of the recruited patients, 19 were male and 11 were female (male: 63%); and of the patients who returned the MEMS bottles, 15 were male and 10 were female (male: 60%). The mean age of patients who did not return the MEMS bottles was 50.5 years (IQR 42-54.5 years) which was around 10 years less than the mean age of those who returned the MEMS bottles: 61 years (IQR 50.25-67.75 years).

4.5.2. Patterns of adherence from MEMS data arising from the feasibility study

The MEMS data obtained from the feasibility study were summarised into six adherence measures. As discussed in Chapter 3, it can be seen that percentage of days with correct dosing takes percentage of too short or too long dosing intervals into account. It also concurrently accounts for a missed dose component. To obtain both the frequency and the occurrence of missed doses, the timeframe of random missed doses per month and drug holidays per 3 months were further considered. Given that percentage of days with correct dosing in conjunction with the frequency and occurrence of missed doses
appears to be a highly informative adherence measure, it is suggested that this adherence measure should primarily be considered in future MEMS studies. With respect to the phases of adherence, this study explored implementation. In addition, based on the observed treatment period for this group of patients, there were no patients with late initiation or early discontinuation.

The importance of percentage of days with correct dosing was emphasised by comparing adherence results calculated by this measure to percentage of dose taken.

Based on MEMS data in this study, it was found that the rule of sixes did not hold true since not one in six patients exhibited each rule. Given the study period, our data could not test rule five and it was not practical to test rule six. Therefore, patterns of adherence observed in this group of patients were reported. The first pattern looked at the most tightened criterion, taking all prescribed doses but timing is fairly inconsistent (taking all doses exactly as prescribed was not considered as it was unlikely); followed by different cut offs of percentage of days with correct dosing (>90%, >80% and 50% to 70%); as well as having 1 to 5 random missed doses for the 1st, 2nd and 3rd month, and having 1 drug holiday per 3 months.

There are some limitations for this study. Firstly, it should be noted that given the small sample size of this study, this study was underpowered to establish the rule of adherence patterns. However, our results should be viewed as exploratory with the consideration of each informative observed pattern of adherence. Secondly, it has been proposed that the first 5 weeks of MEMS records should be discarded to allow a patient’s drug taking behaviour to return to normal behaviour [99, 100]. Given this feasibility study had a relatively short monitoring period of within 1 to 3 months, it was not feasible to discard the first 5 week data. In addition, it was observable in our data that each patient’s adherence pattern did not obviously vary between the first month and the rest of monitoring period i.e. each patient seemed to have his/her individual trend over the entire period. Therefore, data from the entire period were considered. Thirdly, findings arising from this feasibility study e.g. recruitment rates could
be specific to the given setting. Fourthly, only two dosing regimens i.e. once daily and twice daily dosing were examined. Finally, as acknowledged in other MEMS studies, it cannot be confirmed whether patients took a dose when opening the bottle. It was not possible to definitely examine this. However, it was ensured that patients understood how to use MEMS appropriately during the recruitment process. In addition, patients had commented in returned questionnaires regarding dates and times of unintentional openings, of inability to take medications due to a surgery, and the issue of different time zones. It is believed that this concern of false openings should be minimal.

4.6. Conclusions

This study has investigated the feasibility of conducting a larger MEMS study in New Zealand with respect to identification of patients, recruitment and retention and patient acceptability. Issues surrounding identification of patients included pharmacists’ perception of a “high risk” drug, blister packing medications and size of pills. Recruitment rate was higher when studied drug classes were not specific. Retention rate was found to be high at 86% in this study. Overall, patients found that MEMS were easy, practical and comfortable to use. In addition, MEMS data obtained from the feasibility study were explored in relation to adherence patterns. It has been emphasised that percentage of days with correct dosing is a highly informative adherence measure. Based on MEMS data in this study, it was found that the rule of sixes did not hold true. However, these results should be viewed as exploratory given the small sample size of this study.
Chapter 5: Quantification of the forgiveness of drugs to imperfect adherence

This chapter is based on the following peer-reviewed publication:

5.1. Context

In Chapter 4, the extent of drug taking behaviour and the pattern that patients deviate from the nominal prescribed schedule have been demonstrated. In this chapter, therapeutic success in relation to adherence patterns will be explored. Adherence with respect to implementation is considered. Suboptimal implementation may be divided into (1) timing variability, (2) random missed doses which are denoted here as non-consecutive missed doses or by chance two consecutive missed doses and (3) a drug holiday i.e. three or more consecutive missed doses [55].

The circumstance of how sensitive therapeutic success is under imperfect adherence is driven by the property known as forgiveness [57]. A forgiving drug would be one in which therapeutic outcomes are robust to common patterns of imperfect adherence. Forgiveness is a function of the duration of action and the dose interval of the drug, conceptually shown as \( F = D - I \). Here \( F \) is forgiveness, \( D \) is duration of action and \( I \) is dose interval [57]. When the duration of action greatly exceeds the dose interval then the drug is considered forgiving [55, 128]. The number of sequentially missed doses that can be missed with a minimal loss of drug effect i.e. a forgiveness index (FI) can be conceptualised as \( FI = \frac{(D - I)}{I} \) [54, 55, 57, 128]. Here the duration of effect (\( D \)) relates to the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug. Since in practice, patients may not take drugs exactly as prescribed, \( I \) which represents the actual dose interval relates to drug taking behaviour. The PK and PD properties can themselves be further subdivided whereby for PK there are intrinsic and extrinsic drug properties and for PD there are drug and system related properties. For example, an intrinsic PK property is a drug with a long half-life in relation to the dosing interval which leads to persistent plasma concentrations, and an extrinsic PK property is an extended-release formulation which provides an apparently longer half-life. A drug related PD property arises when a given dose yields concentrations that are much higher than the concentration resulting in half maximal effect such that the effect is prolonged.
for longer than would be expected given the declining plasma drug concentrations. A system related PD property pertains to an effect of the drug on the turnover of a substrate in the system for which the half-life of turnover exceeds the dose interval.

The variability in both the duration of action and adherence behaviour should be considered when determining the forgiveness properties of any drug. To date, no studies have considered variability in the PKPD process in conjunction with imperfect adherence patterns in order to develop a comparative criterion to determine the forgiveness of a drug.

5.2. Aims

The aims of this chapter are to (1) develop a criterion to quantify forgiveness, (2) illustrate the criterion for a theoretical example and (3) apply the criterion to warfarin as a motivating example. Warfarin was chosen as it is commonly prescribed and a great deal has been studied about its PKPD properties which allows for interpretation of the clinical importance of forgiveness.

5.3. Methods

Initially a criterion for quantifying forgiveness is introduced, then the methods for exploring the illustrative example and the motivating example for warfarin are described. All simulations in this study were conducted in MATLAB® R2012a (The MathWorks™ Inc., Natick, USA). For both parts 1 and 2 of the methods, all simulations included 1000 individuals each with an individual profile and individual set of PKPD parameters. Note that the adherence profiles were considered to be independent of the PKPD parameter values, such that and for example high or low clearance (CL) values were as likely to accompany a highly adherent profile as a profile representing poor adherence. Relaxation of this assumption will provide opportunities for further exploration of relative forgiveness. The relationship between adherence profiles and PKPD parameter values would be an interested area for future study.
5.3.1. **Quantification of forgiveness as relative forgiveness**

A criterion to quantify forgiveness was developed. Its concept is in-line with relative forgiveness (RF), which has the same interpretation as an odds ratio or relative risk. Calculation of RF was based on the probability of therapeutic success given imperfect adherence ($P_{ip}$) and the probability of therapeutic success given perfect adherence ($P_p$). RF is defined as the number of times more likely that target success is attained under perfect adherence compared to imperfect adherence; or when comparing two drugs under a standard setting of imperfect adherence.

A general form of relative forgiveness is given by, $RF$:

$$RF = \frac{P_{ip}/(1 - P_{ip})}{P_p/(1 - P_p)}$$

*Equation 5.1: A general form of relative forgiveness*

where $RF$ is the relative forgiveness, $P_{ip}$ is the probability of successful attainment of a treatment target under imperfect adherence, and $P_p$ is the probability of successful attainment of a treatment target under perfect adherence. Values of RF close to one indicate that a drug is forgiving to imperfect adherence and values close to zero indicate that the drug is particularly sensitive to imperfect adherence behaviour (i.e. not forgiving).

When comparing the RF of two drugs (Drug A and Drug B) then the relative forgiveness of drug B compared to drug A can be determined as:

$$RF(B:A) = \frac{P_{ip}[B]/(1 - P_{ip}[B])}{P_{ip}[A]/(1 - P_{ip}[A])}$$

*Equation 5.2: The relative forgiveness of Drug B compared to Drug A*

In this setting Drug A and Drug B could be two formulations of the same drug or could be different drugs. When comparing drugs then values of RF can exceed 1 and, in this circumstance, indicate how many times more likely that drug B is forgiving compared to drug A (i.e. how many times more likely therapeutic success will be achieved with drug B compared to drug A) given some pattern of imperfect adherence.
5.3.2. Illustration of the forgiveness criterion with a theoretical example

5.3.2.1. PKPD model

A 1-compartment instantaneous unit input PK model linked to an immediate effects $E_{\text{max}}$ PD model was used as an illustrative example (as per, for example [222, 223]). Two scenarios were considered (1) perfect adherence, (2) imperfect adherence which consisted of several subtypes of imperfect adherence patterns. In these scenarios, a 1 unit dose was administered every half-life for 150 half-lives. Steady state was assumed at 10 half-lives. The model is shown in Table 5.1. Proportional residual variability was incorporated to the effect.

**Table 5.1: Model for a theoretical example**

<table>
<thead>
<tr>
<th>Parameter/variable*</th>
<th>Mean value</th>
<th>BSV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CL (L/d)</td>
<td>$\ln(2)^*$</td>
<td>30</td>
</tr>
<tr>
<td>V (L)</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>$EC_{50}$ (mg/L)</td>
<td>1.3</td>
<td>30</td>
</tr>
<tr>
<td>Proportional RUV</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

CL is clearance. $V$ is apparent volume of distribution. $E_{\text{max}}$ is maximum effect. $EC_{50}$ is drug concentration resulting in half maximal effect. BSV is between subject variability. RUV is residual unexplained variability.

* Note the units are arbitrary and provided for interpretation of once daily dosing profiles.

* This value was chosen to provide a half-life of 1 unit.

5.3.2.2. Parametric simulation of imperfect adherence patterns

In this work adherence patterns were simulated from parametric distributions. It is noted in the work of others that various approaches have been used to estimate imperfect adherence including Bayesian approaches and Markov models [112, 224-228]. These techniques were not considered in this study since the goal was to simulate acceptable patterns of non-adherence rather
than to learn about how patterns of non-adherence arise. Simulated patterns were used to assess the relative forgiveness criterion and its performance.

The three types of imperfect adherence patterns were considered that when layered together would provide an overall imperfect adherence pattern. These were (1) timing variability, (2) random missed doses and (3) drug holidays.

An index adherence profile that included the imperfect adherence patterns described above was identified from an online resource, www.iAdherence.org. The index adherence profile was identified that had once daily dosing prescribed for 150 days (see Figure 5.1). The profile was compared to other once daily profiles and was determined to contain typical features and importantly contained all the three key patterns of interest but did not contain initiation or discontinuation aspects of non-adherence.

![Index Adherence Profile](https://www.iAdherence.org)

**Figure 5.1:** An index adherence profile. The X-axis is calendar date in day/month/year. The Y-axis is 24 hour clock time. Each dot represents timing of each dose taken. Each vertical bar depicts each missed dose. (Figure taken from www.iAdherence.org)

After identifying the index adherence profile, this index profile was then used to quantify important features of each imperfect adherence pattern. The important features were used to determine reasonable parametric distributions of the three sources of imperfect adherence (timing variability, random missed doses and drug holidays). Figures 5.2, 5.3 and 5.4 show the parametric
distribution of timing variability, random missed doses and drug holidays, respectively. Full details are included in Appendix A.3.1.

**Figure 5.2:** Parametric distribution of timing variability. This distribution is provided by a mixture of 2 normals. The X-axis represents the difference of the actual dose time from the nominal dose time (hours). The Y-axis is density.

**Figure 5.3:** Poisson distribution of random missed doses. The X-axis is number of random missed doses. The Y-axis is density.
5.3.2.3. Successful attainment of a treatment target

The profile of the drug effect for each individual was assessed for successful attainment of a target treatment. Only steady state profiles were considered and the first 10 dosing profiles were discarded (corresponding to 10 half-lives of maintenance doses) over the period of 150 days. For the purposes of these simulations, successful attainment of a target was defined as:

1. The effect level at the trough was greater than a defined lower treatment target. The (hypothetical) threshold of a target success is illustrated in Figure 1 using an individual with the mean values of CL, V, $E_{\max}$, $E_{50}$.

2. The number of doses where criterion 1 is true meets a defined fraction of doses over the 140 treatment doses.

It should be noted that (1) is sensitive to variability in both PKPD and adherence profiles whereas (2) is most sensitive to variability in adherence. For the theoretical example, the value for (1) was set to a minimum trough effect value of 0.35 (units) and the value for (2) was 0.9 such that at least 90% of doses (from dose 11) within an individual must have an effect at the trough greater than 0.35 (units).

To evaluate the forgiveness criterion, the success of target attainment for each simulated patient was evaluated with a perfect adherence profile and an imperfect adherence profile. Summing the success values and expressing as a
fraction of the 1000 patients provides the probability of success for either perfect adherence \( (P_p) \) or imperfect adherence \( (P_{ip}) \). This is shown in the following 4 steps using warfarin as an example:

5.3.2.3.1. **Success for an individual patient at a particular dosing interval**

For the \( i \)th patient receiving warfarin the successful (s) attainment of an International Normalised Ratio (INR) for the \( j \)th dose is given by,

\[
s_{ij}(INR) = \begin{cases} 
0, & \text{if} \ \text{through}_{ij}(INR) < 2 \ \text{or} \ \text{through}_{ij}(INR) > 3.5 \\
1, & \text{if} \ 2 \leq \text{through}_{ij}(INR) \leq 3.5 
\end{cases}, \text{for} \ j > 20
\]

*Equation 5.3: Success for an individual patient at a particular dosing interval*

where \( s_{ij}(INR) \) is an indicator variable that takes the value of 1 if the observed INR is in the therapeutic range and 0 otherwise. In this example, the first 20 doses are discarded as these were not considered to be within 90% of steady state.

5.3.2.3.2. **Time in the therapeutic range**

The proportion of dose intervals within the therapeutic range \( (TTR_i) \) for the \( i \)th individual is determined by the number of successful doses that arise from (1) above as a fraction of the total number of doses under consideration. Each patient receiving 130 doses was considered.

\[
TTR_i = \frac{\sum s_{ij}(INR)}{130}
\]

*Equation 5.4: Time in the therapeutic range*

5.3.2.3.3. **Overall success for a patients dosing regimen**

The dosing regimen with associated PKPD and adherence variability was considered to be a success \( (S_i) \) when the number of successful dose intervals exceeded the predefined criteria (for warfarin this was; \( fd = 0.55 \)). The value of 1 indicates success and 0 otherwise.

\[
S_i = \begin{cases} 
TTR_i > fd \\
0, & \text{when} \ TTR_i < fd \\
1, & \text{when} \ TTR_i \geq fd
\end{cases}
\]

*Equation 5.5: Overall success for a patients dosing regimen*
5.3.2.3.4. Probability of success for 1000 patients

The probability of success is the fraction of successful patient profiles out of the total number of simulations.

\[
P = \frac{1}{1000} \sum_{i=1}^{1000} S_i
\]

Equation 5.6: Probability of success for 1000 patients

where \( P \) is the probability of success for either perfect adherence (\( P_p \)) or imperfect adherence (\( P_{ip} \)).

5.3.2.4. Influence of different types of imperfect adherence on RF

The influence of imperfect timing and missed doses (random missed doses + drug holidays) were considered separately and when combined into the overall composite pattern. In addition, a series of what-if scenarios were investigated in which hypothetical drugs were considered that had the following characteristics: (i) a longer half-life (the value of CL halved) [DRUG B], (ii) greater potency (EC\(_{50}\) halved) [DRUG C], (iii) a combination of longer half-life and greater potency (both CL and EC\(_{50}\) halved) [DRUG D] and (iv) where the dose was doubled [DRUG A x 2].

5.3.3. Application of the forgiveness criterion to warfarin

Adherence patterns were simulated using the same methods as described for the illustrative example. For this warfarin example, 1000 individuals were simulated with perfect and imperfect adherence profiles.

The model used for warfarin in this study was a population kinetic-pharmacodynamic (KPD) model developed by Hamberg et al. [229]. The model and parameter values are taken from [229] and are provided in Appendix A.3.2. The dose was 3.5 mg given once daily for 150 days. The dose was chosen such that the population average patient with perfect adherence would achieve a steady state average INR midway in the therapeutic range. Successful attainment of a treatment target was considered as time in the therapeutic range. The time to steady state was assumed to be 20 days. The therapeutic range was defined as
Chapter 5: Quantification of forgiveness of drugs to imperfect adherence

an INR within the range of 2 to 3.5. Successful treatment was defined as where at least 55% of steady state trough values were within the therapeutic INR range (which is similar to the success reported by Wright & Duffull [230] when INR monitoring was not performed). Note that in this example dose individualisation to target INR was not considered. Covariates were not considered and it was assumed that food had no impact on INR.

5.4. Results

The results are divided into two parts: 1) illustration of the forgiveness criterion with a theoretical example and 2) an application of the criterion to warfarin.

5.4.1. Illustration of the forgiveness criterion with a theoretical example

Considering the same individual with the typical values of CL, V, E_{\text{max}}, \text{EC}_{50} (mean values), Figure 5.5 shows a comparison of the PK and PKPD responses to perfect and imperfect adherence.

Figure 5.5: A comparison of a single individual with perfect adherence (left panel) and imperfect adherence (right panel) with the top row representing the adherence profile, the second row the concentration-time profile and the third row the effect-time profile.
5.4.1.1. Quantification of forgiveness as relative forgiveness

For the illustrative example, the probability of target attainment with imperfect adherence \(P_{ip}\) was 0.38 and the probability of target attainment with perfect adherence \(P_p\) was 0.62 yielding a relative forgiveness (RF) of 0.38. This means that therapeutic success was 0.38 times as likely (i.e. 62% less likely) with imperfect adherence. When profiles were considered that only contained timing errors the RF was 0.80 and when only considering missed doses (random missed doses and drug holidays) the RF was 0.44. It is clear that missed doses, from any cause, have a quantitatively larger effect on RF than timing errors. Indeed the influence on timing errors resulted in only a 20% reduction in RF indicating that in this example timing is of minimal concern.

The original drug properties are shown in Table 5.1. Changes in drug properties resulting in different values of RF are presented in Table 5.2. Here the relative forgiveness is a comparison of the different drug properties (DRUG B, C, D, A x 2) to the original drug properties (termed DRUG A).

### Table 5.2: Theoretical modifications to the drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>(P_{ip})</th>
<th>RF(B: A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG A (original drug)</td>
<td>0.38</td>
<td>-</td>
</tr>
<tr>
<td>DRUG B (twice half-life)</td>
<td>0.84</td>
<td>8.57</td>
</tr>
<tr>
<td>DRUG C (twice potency)</td>
<td>0.69</td>
<td>3.63</td>
</tr>
<tr>
<td>DRUG D (twice half-life and twice potency)</td>
<td>0.95</td>
<td>31</td>
</tr>
<tr>
<td>DRUG A x 2 (double dose)</td>
<td>0.71</td>
<td>3.99</td>
</tr>
</tbody>
</table>

The results showed that when compared to the original drug with imperfect adherence that increasing the half-life had the greatest single effect, becoming almost 9 fold more forgiving. Changing half-life and potency together yielded a marked (31 fold) increase in forgiveness. This value from the simulations was also similar to the value from the product of the two independent effects, changing half-life RF = 8.57 and changing potency RF = 3.63.
Doubling the dose was similar in effect size to doubling potency (i.e. halving EC$_{50}$) in this simulated example.

5.4.2. Application of the forgiveness criterion to warfarin

Simulations with warfarin included all components of imperfect adherence, i.e. imperfect timing, missed doses and drug holidays. The probability of therapeutic success for perfect adherence was 0.58 and for imperfect adherence was 0.52. The relative forgiveness of warfarin to imperfect adherence was 0.78, which indicates that success was 22% less likely with warfarin for imperfect adherence, suggesting that warfarin is a relatively forgiving drug to non-adherence originating from factors linked to implementation.

5.5. Discussion

This study has described a criterion to quantify forgiveness that accounts for variability in both PKPD and adherence. The criterion as relative forgiveness (RF) has been defined which has the same interpretation as an odds ratio or relative risk. The RF holds the original concept of forgiveness while incorporating variability in the duration of drug action as well as the dose interval. This criterion can be used to compute the forgiveness of a given drug or to compare the forgiveness between two drugs whose effects can be quantified on the same biomarker of response. This study shows how the proposed criterion can be used to determine forgiveness for a specific drug, to compare between drug entities that have different pharmaceutical and/or pharmacological profiles and how it can be applied to a current therapeutic agent, namely warfarin.

The concept of forgiveness has been considered previously [166, 224, 231-234]. In a study of Alzheimer’s disease it was reported that, under chronic dosing, one or two consecutive missed dose/s of donepezil 5 mg or 10 mg would be unlikely to affect the attainment of the optimal target of peripheral cholinesterase inhibition [233]. Similarly, it has been shown that the
administration of either once or twice daily lopinavir/ritonavir resulted in comparable treatment outcomes [235]. Later research on lopinavir/ritonavir found that the proportion of patients achieving appropriate virologic suppression over 24 weeks were similar across four quartiles of adherence rates, measured as percentage of prescribed doses taken, ranging from 23.5-53.3% to 92.9-100% [166]. In addition, the degree of forgiveness of hypertensive drugs has been established based on “off-rate”, e.g. loss of a decrease in blood pressure in mmHg per day under imperfect adherence circumstances [224]. These findings indicate that drugs are forgiving when they have low off-rates i.e. drugs with a long duration of action. Examples of low off-rate antihypertensive drugs that are administered once daily included amlodipine and aliskiren and examples of those with high off-rates including enalapril and atenolol [129, 224]. These measures to date have considered forgiveness informally and attempted to find drug related characteristics that are associated with forgiveness.

Recently the work of Boissel and Nony has provided a theoretical framework for quantification of forgiveness [236]. Their work considered alteration of PKPD parameters of direct and delayed models of hypothetical drugs to explore impact on drug effects [236]. Our study, and criterion, builds on this approach and also incorporates variability in the PKPD parameters. Nony and Boissel further proposed the use of sensitivity functions to compare forgiveness [237]. Methods for comparing forgiveness across drugs were also investigated by Gohore et al. [225]. In this study the most sensitive PKPD parameters in relation to the number of subtherapeutic days and smoothness index were determined and forgiveness was based on a sensitivity analysis and a comparison of four calcium channel blocker drugs [225]. This work did not consider forgiveness in the context of concurrent variability in adherence and PKPD parameter values.

With respect to the influence of different types of imperfect adherence on forgiveness, it was found that the influence of only missed doses was stronger than that of only timing variability with RF values of 0.44 and 0.80, respectively (in our theoretical example). This finding is not surprising since most drugs have
a duration of action that spans more than a few hours either side of the nominal
dose interval and hence timing variability is likely to be quantitatively less
important. This effect will be drug specific and drug candidates that have poor
forgiveness to timing variability are likely to fare much worse in RF values. It
may be expected that the influence of timing variability will be more influential
if the distribution of timing variability deviates to a much larger extent compared
to the timing variability used in this study. However, it is believed that the
greatest impact of timing variability would be seen in the most extreme timing
variability i.e. random missed doses, which is categorised separately as in this
case not only is timing delayed but the dose is also not taken. In general, it
therefore seems that the number of random missed doses is a more influential
adherence pattern than the timing of any given dose. It is also proposed that the
influence of missed doses depends also on the dosing schedule. For instance, it
has been proposed that drug actions may persist longer in patients prescribed
with twice daily compared to once daily dosing since the probability of missing
two or three consecutive doses in the former is proposed to be half of that of
missing a daily dose in the latter [238]. To illustrate, in terms of the maintenance
of drug concentrations within a therapeutic range, which may well result in the
maintenance of drug actions, twice daily lopinavir/ritonavir was reported to be
superior to once daily lopinavir/ritonavir [238]. A corresponding result has been
shown with saquinavir/ritonavir [232] and again similarly for twice daily
ticagrelor compared to once daily clopidogrel [109].

Our work has shown how theoretical modifications to the properties of a
drug (either by chemical alteration or pharmaceutical modification) can be
quantified in terms of an alteration in forgiveness. A drug with twice the potency
or given at twice the dose shared similar degrees of relative forgiveness (both
had RF values around 4 in the theoretical example). By comparison, a drug with
twice the half-life was considerably more forgiving (an RF of approximately 8 in
the theoretical example). A combination of longer half-life and greater potency
combined linearly to provide a relative forgiveness of approximately 30 (the
product of the influence of either modification alone). Choice of drug, either in
drug development to consider which lead molecule to take forward, or in therapeutics to consider which medicine to use in a patient with known poor adherence, can therefore account a priori for the likely influence of its forgiveness. All things being equal then a drug with the best relative forgiveness should be considered.

The RF criterion was illustrated by consideration of warfarin. The therapeutic range was chosen to be an INR between 2 and 3.5 and therapeutic success defined when at least 55% of a dosing profile achieved INR values in that range. For simplicity, this example did not consider dose individualisation of warfarin dose to achieve the INR target since this example is to show an application rather than a definitive review of warfarin forgiveness. Under imperfect adherence, the value of RF was not diminished greatly from 1 (RF=0.78). In theory a confidence interval could be applied to this quantity but this would have natural statistical limitations on its interpretation since the interval (for the same drug) cannot include the null value. The high value of RF for warfarin indicates that the likelihood of patients with suboptimal adherence (comprising timing variability, random missed doses and random drug holidays) successfully attaining the target was 0.78 times of those with perfect adherence. Hence, the impact of imperfect adherence on achieving a desirable INR was considered minimal. It seems likely, therefore, that under profiles of imperfect adherence that are within the range of plausible profiles explored here that warfarin would remain forgiving. A plausible poor adherence scenario that would have been included in these simulations would have had 3 drug holidays and 25 missed doses over the 150 treatment day period.

It should be noted that the index adherence pattern chosen for this study was not related specifically to anticoagulants and it is possible that adherence patterns may differ in patients with atrial fibrillation or coagulation disorders due to the influence of disease or other patient characteristics (e.g. age). Although it is possible that adherence patterns, and hence forgiveness values, may differ depending on the subpopulation being studied, our index adherence profile has been compared to other adherence profiles and it is postulated that
the adherence implementation features that were seen in the index profile are representative of other profiles. In this work it was assumed that the adherence profile of a patient was independent of the PKPD parameters. This assumption is not a requirement of determining RF but was rather a simplification used here in these examples. It is plausible that an association between adherence patterns and PKPD profiles may exist where an association between patient covariates, e.g. age and adherence patterns has been identified previously (as per [112]). If it were the case that either a PK parameter, e.g. CL, or PD parameter, e.g. $E_{\text{max}}$, were correlated with age then there may be an association between adherence patterns and PKPD parameters. However, as mentioned in the methods section: Parametric simulation of imperfect adherence patterns, the purpose of this current work was not to learn how patterns of non-adherence arise but rather provide a forgiveness criterion. The influence of covariates would be an important and interesting further exploration. It is also noted that this study focused on the process of suboptimal implementation rather than failure to initiate or early discontinuation. Here the concept of forgiveness is articulated in the case where implementation and its issues predominates. However patients who fail to initiate, while an important population for consideration, are not amenable to choice of forgiving regimens in circumstances when patient autonomy is maintained. Finally, this work illustrated the case of once daily drug administration. Therefore, it should be noted that for other dosing regimens, profiles of imperfect adherence would differ. However, the RF criterion described in this paper is generalisable to these settings.

5.6. Conclusions

In conclusion, this study shows that relative forgiveness can be used as an index to quantify the forgiveness properties of a drug given its dosing regimen. This may have important implications for both drug development and clinical practice. Further work is needed to examine the properties of RF as a measure of forgiveness behaviour to determine its clinical utility.
Chapter 6: Application of relative forgiveness using clinically observed adherence profiles

This chapter will form the basis for a publication that will be submitted as:

6.1. Context

In the previous chapter, a relative forgiveness (RF) criterion was developed to quantify the forgiveness of drugs. The evaluation of relative forgiveness was then shown with warfarin as a motivating example. It is proposed that relative forgiveness is generalisable to any given drugs to quantify their forgiveness properties under the presence of imperfect adherence. In this chapter, relative forgiveness will be applied to actual patients’ adherence data and dosing for the two drugs in the Medication Event Monitoring System (MEMS) feasibility study presented in Chapter 4.

The two selected drugs in this study are atorvastatin and omeprazole. Both statins and proton pump inhibitors (PPIs) are commonly prescribed and there has been a considerable body of research establishing their therapeutic benefits. In addition, atorvastatin and omeprazole represent drugs used for prevention of disease and for treatment of symptomatic disease, respectively, which may influence adherence differently. For example, it has been reported that the percentage of patients who persisted with PPIs prescriptions, for 6 months, 1 year and 2 years, was higher among the indications of severe gastro-oesophageal reflux disorder (GORD) or Barrett’s oesophagus compared to less severe indications such as non-reflux dyspepsia or Helicobacter pylori associated indications [239]. This suggests that given that adherence patterns are likely to be different, drugs may be more or less forgiving depending not only on the basis of their pharmacokinetic-pharmacodynamic (PKPD) properties but also on the patient’s response to negative symptoms.

PPIs block gastric acid secretion by binding irreversibly to the H+K+ATPase enzyme, proton pumps, in parietal cells. Their therapeutic use includes the treatment of gastric ulcers, duodenal ulcers, GORD, Zollinger-Ellison syndrome, Barrett’s oesophagus and Helicobacter pylori infection as part of a combination therapy. Evidence of the effect of PPIs on various indications including comparison among drugs within the class has been established, as per these reviews [240, 241]. PPIs are prodrugs with the core structure of benzimidazole
with a substituted 2-(pyridine methylsulfinyl group). The prodrug is metabolised under acid conditions to the active sulfenamide. The sulfenamide then forms a covalent disulphide bond with cysteine on the proton pump and acid secretion is inhibited.

Statins inhibit HMG-CoA reductase enzyme preventing the conversion of HMG-CoA to mevalonate the rate limiting step in the production of cholesterol. The downstream production of cholesterol is then inhibited. Statins are used to prevent and treat cardiovascular and coronary heart disease (primary and secondary prevention, respectively). Several clinical trials and meta-analyses have demonstrated the benefits of statins for both primary and secondary prevention, including [242-250]. It has been reported that adherence measured by discontinuation rate was higher among patients with primary prevention, compared to those with existing coronary artery disease and acute coronary syndrome [251]. Another study has also reported that persistence after 6 months and 3 years was lower in patients with primary compared to secondary prevention [252].

In the previous chapter, adherence variability was accounted for by generating imperfect adherence profiles from an index adherence profile with variability being incorporated. This is under the circumstance that a patient’s actual adherence profile is unknown. In the more specific circumstance where each patients’ drug taking behaviour is individually identified such as in this work, the relative forgiveness criterion can also be used to quantify an RF of each patient given their own drug taking behaviour. If MEMS type devices were used in clinical practice then it would be possible to explore implications of poor adherence for individual patients.

6.2. Aims

The aim of this study is to quantify an RF of each patient prescribed 1) atorvastatin or 2) omeprazole, given their own clinically observed adherence profile.
6.3. Methods

In this chapter, the developed relative forgiveness criterion outlined in Chapter 5 was used with atorvastatin and omeprazole. The methods consist of two main parts that characterise atorvastatin and omeprazole. For each drug, the methods are divided into five parts: (1) identification of a population PKPD model, (2) extraction of clinically observed adherence profiles, (3) parametric simulation of PKPD profiles for each patient, (4) quantification of attainment of a treatment target and (5) visualisation of the time course of drug effect profile. All simulations in this study were conducted in MATLAB® R2013b (The MathWorks™ Inc., Natick, USA).

6.3.1. Atorvastatin

6.3.1.1. Identification of a population PKPD model

Since there were no published population PKPD models for atorvastatin, a published population PK model for atorvastatin acid and its lactone metabolite [253] linked to a published population PD model for simvastatin [254] was used in this study. The PK model was developed by Narwal et al. [253]. The PD model was part of the population PKPD model for simvastatin originally developed by Kim et al. [254].

The PK model described the parent drug, atorvastatin acid, and its active metabolite, atorvastatin lactone. Atorvastatin acid was described by a two-compartment disposition model with first-order absorption. Atorvastatin lactone was described by a one-compartment model. Based on the work of Jacobsen et al. [255], it was assumed that atorvastatin acid and atorvastatin lactone interconverted. In this work atorvastatin acid concentration was chosen as the driver for the PD model (see Figure 6.1).

Atorvastatin PK model parameter values are taken from [253] and are provided in Table 6.1.
Table 6.1: Atorvastatin PK model parameters [253]

<table>
<thead>
<tr>
<th>PK model parameter</th>
<th>Population estimate</th>
<th>BSV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_a$ (/h)</td>
<td>3.5</td>
<td>-</td>
</tr>
<tr>
<td>$CL_{pm}$ (L/h)</td>
<td>504</td>
<td>34.4</td>
</tr>
<tr>
<td>$V_1$ (L)</td>
<td>3250</td>
<td>67.1</td>
</tr>
<tr>
<td>$V_2$ (L)</td>
<td>2170</td>
<td>19.7</td>
</tr>
<tr>
<td>$Q$ (L/h)</td>
<td>1880</td>
<td>-</td>
</tr>
<tr>
<td>$CL_m$ (L/h)</td>
<td>116</td>
<td>45.1</td>
</tr>
<tr>
<td>$V_3$ (L)</td>
<td>137</td>
<td>70.1</td>
</tr>
<tr>
<td>$CL_{mp}$ (L/h)</td>
<td>24</td>
<td>-</td>
</tr>
</tbody>
</table>

$k_a$ = absorption rate constant, $CL_{pm}$ = CL of the parent drug (atorvastatin acid) to the metabolite (atorvastatin lactone), $V_1$ = $V$ of the parent drug in the central compartment, $V_2$ = $V$ of the parent drug in the peripheral compartment, $Q$ = intercompartmental clearance of the parent drug, $CL_m$ = CL of the metabolite, $V_3$ = $V$ of the metabolite, $CL_{mp}$ = CL of the metabolite to the parent drug. Bioavailability was assumed to be 1.

The effect of atorvastatin acid concentration on the production rate of low-density lipoprotein (LDL), $R_{in}$, was explained by the inhibitory turnover model, the PD model used here.

The atorvastatin PKPD model is given by:

$$\frac{dLDL}{dt} = R_{in} \times \left[1 - \frac{E_{max} \times C(t)}{C_{50} + C(t)}\right] - k_{out} \times LDL$$

$$LDL_0 = LDL\ \text{baseline and} \ E_{max} \ \text{is constrained as,} \ 0 < E_{max} < 1$$

Equation 6.1: The atorvastatin PKPD model

For simplicity, circadian variability for the production of LDL was not considered in this study. It is noted that the influence of amplitude on the $R_{in}$ value is $<10\%$ [132] of the value for production and hence it is likely to be of limited clinical importance.

As previously discussed, the PD model used was that for simvastatin. Simvastatin PD model parameter values are taken from [254] and are provided in Table 6.2 [254]. Since the population PKPD model for simvastatin was developed based on healthy volunteer data, in this work, LDL concentration
baseline was set as 4.78 mmol/L (185 mg/dL), based on the Scandinavian Simvastatin Survival Study [242]. Between subject variability (BSV) was incorporated to the LDL concentration baseline as 20.2 CV% as per the value reported by Kim et al. [254].

**Table 6.2: Simvastatin PD model parameters**

<table>
<thead>
<tr>
<th>PD model parameter</th>
<th>Population estimate</th>
<th>BSV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL baseline (mg/dL)</td>
<td>185</td>
<td>20.2</td>
</tr>
<tr>
<td>R_in (mg/dL/h)</td>
<td>1.14</td>
<td>-</td>
</tr>
<tr>
<td>E_max</td>
<td>0.489</td>
<td>-</td>
</tr>
<tr>
<td>C_{50} (ng/mL)</td>
<td>0.0868</td>
<td>-</td>
</tr>
<tr>
<td>k_out</td>
<td>R_{in}/LDL baseline</td>
<td>-</td>
</tr>
</tbody>
</table>

\( R_{in} = \) production rate of LDL, \( E_{max} = \) maximum effect, \( C_{50} = \) the plasma concentration resulting in half maximum effect, \( k_{out} = \) elimination rate constant of LDL.

Apart from the LDL concentration baseline, there were no other BSV values incorporated into PD model parameters as per the study of Kim et al. Residual variability was not incorporated in this study since the goal was to determine successful attainment of the true effect rather than successful attainment of an observed effect.

It is noted that atorvastatin is slightly more potent than simvastatin with \( C_{50} \) values of 8.2 nM and 11.2 nM for atorvastatin and simvastatin, respectively [256]. The difference was considered negligible in this work and hence the \( C_{50} \) value for simvastatin was chosen. It is likely therefore that this work may slightly underestimate the relative forgiveness of atorvastatin as per the findings from Chapter 5. It should be noted that the \( C_{50} \) values arise from healthy volunteers rather than patients.
Chapter 6: Application of relative forgiveness using clinically observed adherence profiles

Figure 6.1: A schematic of PKPD model for atorvastatin. $k_a =$ absorption rate constant, $CL_{pm} =$ CL of the parent drug (atorvastatin acid) to the metabolite (atorvastatin lactone), $V_1 =$ $V$ of the parent drug in the central compartment, $V_2 =$ $V$ of the parent drug in the peripheral compartment, $Q =$ intercompartmental clearance of the parent drug, $CL_m =$ CL of the metabolite, $V_3 =$ $V$ of the metabolite, $CL_{mp} =$ CL of the metabolite to the parent drug, $R_{in} =$ production rate of LDL, $k_{out} =$ elimination rate constant of LDL. Adapted from Narwal et al. [1] and Kim et al. [2].

Subsequently, two scenarios were considered (1) perfect adherence and (2) imperfect adherence.

The dose prescribed for each patient was:

1) Patient 17: 40 mg  
2) Patient 19: 80 mg  
3) Patient 23: 10 mg

All three patients were prescribed once daily for 90 days (for this current medication refill).
6.3.1.2. Extraction of clinically observed adherence profiles

In Chapter 4, there were three patients prescribed atorvastatin (Patients 17, 19 and 23). Each clinically observed adherence profile is depicted as follows (Figures 6.2, 6.3 and 6.4, respectively):

**Figure 6.2:** Clinically observed adherence profile of Patient 17

**Figure 6.3:** Clinically observed adherence profile of Patient 19

**Figure 6.4:** Clinically observed adherence profile of Patient 23

The number of random missed doses and drug holidays over the treatment period of 90 days for each patient is summarised in Table 6.3. Drug holidays here are defined as three consecutive missed doses.
Table 6.3: Number of missed doses over the 90 treatment day period for each patient prescribed atorvastatin

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Random missed doses</th>
<th>Drug holidays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 17</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Patient 19</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Patient 23</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

The number of random missed doses observed in Patient 17 is around the mean value of those in Chapter 5 (random missed doses = 13). Drug holidays observed in these three patients share similarities with the drug holiday distribution in Chapter 5.

6.3.1.3. Parametric simulation of PKPD profiles for each patient

Since the PKPD parameter values cannot be observed in each individual, it is impossible to calculate an individual value of relative forgiveness for each patient taking atorvastatin. Therefore, 1000 sets of individual PKPD parameters were simulated under these 2 scenarios: (1) a perfect adherence profile with the prescribed dose and (2) each observed imperfect adherence profile with the corresponding prescribed dose for each patient. The probability of therapeutic success given perfect adherence \( P_p \) and the probability of therapeutic success given imperfect adherence for each patient \( P_{ip} \) were calculated. RF for each patient was then determined.

6.3.1.4. Qualification of attainment of a treatment target

The time to steady state was assumed to be 20 days. Therefore, the first 20 days were discarded and not included in determination of RF. This relatively long period of 20 days was chosen to ensure that steady state was achieved in all scenarios such as patients having extreme PK characteristics e.g. extreme values of clearance or \( k_{out} \). Successful attainment of a treatment target was considered as time below the therapeutic criterion. The therapeutic criterion was defined as an LDL concentration of 2.6 mmol/L. Successful treatment was defined as where
at least 60% of steady state trough values were below the therapeutic LDL criterion.

6.3.1.5. Visualisation of the time course of drug effect profile

To visualise the time course of drug effect, the LDL vs time profile for an average patient with mean population parameter estimates was simulated under each observed imperfect adherence as well as perfect adherence at each prescribed dose.

6.3.2. Omeprazole

6.3.2.1. Identification of a PKPD model

Since no published population PKPD models were found for omeprazole, a published PKPD model for lansoprazole developed by Puchalski et al. [257] was used in this study. Sulfenamide forms of omeprazole and lansoprazole bind cysteine 813 and 892; and cysteine 813 and 321 at the proton pump, respectively. These cysteine locations are differentially accessible to reducing agents which can cleave the sulfenamide resulting in recovery of acid secretion that occurs more rapidly than de novo synthesis of proton pumps [258]. Further details are explored in the discussion section. Based on this, the PKPD characteristics of omeprazole and lansoprazole appear to be similar then the choice of lansoprazole would seem, in the initial setting, to be reasonable.

The lansoprazole PKPD model can be depicted into three compartments as shown in Figure 6.5. The schematic comprises 1) plasma lansoprazole concentration compartment, 2) a compartment representing $\text{H}^+ /\text{K}^+ \text{-ATPase}$ enzyme (proton pump) and 3) a compartment representing hydrogen ions (gastric acid).

The PK model was originally described by a one-compartment Bateman model with absorption lag time [257]. However, the authors stated that since the absorption rate constant was much larger than the elimination rate constant then they simplified the model to a monoexponential function with absorption lag time [257], shown as:
\[ C(t) = \frac{D}{V} \exp\left( -\frac{CL}{V} \times t - t_{lag} \right) \]

*Equation 6.2: The PK model for lansoprazole*

**Figure 6.5:** A schematic of the PKPD process of lansoprazole. C = concentration compartment, E = H\(^+\)/K\(^+\)-ATPase Enzyme (proton pump) compartment, H = Hydrogen ions (gastric acid) compartment, \( k \) = elimination rate constant of lansoprazole, \( R_{\text{in}E} \) = production rate of proton pumps, \( k_d \) = first elimination rate constant of proton pumps, \( k_{\text{deg}} \) = second elimination rate constant of proton pumps, \( R_{\text{in}H} \) = production rate of gastric acid, \( k_{\text{out}} \) = elimination rate constant of gastric acid. Adapted from Puchalski et al. [257].

Considering the proton pump compartment, there are two processes of elimination of proton pumps (see Equations 6.3 and 6.4): (1) the elimination due to irreversible binding of between the drug (active forms of sulfenamide) and proton pumps, which is described by the first elimination rate constant (\( k_d \)), (2) natural degradation of proton pumps at the rate of \( k_{\text{deg}} \) (excluding the natural degradation of proton pumps causing by \( k_d \) when lansoprazole is not present). The concentration from the first compartment is a driver to stimulate the elimination of proton pumps here.
\[
\frac{dE}{dt} = R_{\text{in}E} - k_{\text{deg}} \times E - k_d \times C \times E
\]

**Equation 6.3: Rate of proton pump production**

Assuming that the baseline amount of proton pumps (\(E_0\)) is 1 and the concentration of lansoprazole is 0 then \(E_0 = \frac{R_{\text{in}E}}{k_{\text{deg}}}\). Here we see that the lansoprazole binds 1:1 with the enzyme. The equation is written was a mass relationship.

Therefore \(R_{\text{in}E} = k_{\text{deg}}\) and the Equation 6.3 becomes:

\[
\frac{dE}{dt} = k_{\text{deg}} - k_{\text{deg}} \times E - k_d \times C \times E
\]

**Equation 6.4: Rate of proton pump production normalised by \(E_0 = 1\)**

Then the change of the amount of proton pumps (\(E/E_0\)) results in an increase of the production of gastric acid in the gastric acid compartment (see Equation 6.5). In the original study, a cosine function was considered for production rate of hydrogen ions. An amplitude on the \(R_{\text{inh}}\) value was 25.3 mM (Group 1 data). Time of peak hydrogen ion production was at 12.6 hours (8:30 pm). For simplicity, \(R_{\text{inh}}\) was set to a mean production rate of hydrogen ions in this study. In addition without knowing the acrophase for each patient then timing-related imperfect adherence aspects are not possible to interpret.

\[
\frac{dH}{dt} = R_{\text{inh}} \times \frac{E}{E_0} - k_{\text{out}} \times H
\]

**Equation 6.5: Rate of gastric acid secretion**

The conversion of hydrogen ions to pH is explained in Equation 6.6. It was assumed that there is a baseline amount of acid in a stomach. This could be conceptualised as a hypothetical condition of a neutral environment where pH=7. Therefore, the effect of the drug results in the change in the ratio of \([H^+]\) and \([OH^-]\). For illustration, at pH=1, the excess ratio of \([H^+]:[OH^-]\) could be calculated as \(10^{(7-1)} = 10^6 \ [H^+]>[OH^-]\). Conversely, at pH= 13, the excess ratio of \([OH^-]:[H^-]\) would be \(10^{(13-7)} = 10^6 \ [OH^-]>[H^+]\). According to Puchalski et al., an
initial pH condition was around 2.2. Given that in this study the effect of food was not considered, an initial pH as 3 was set which is a similar value observed when food was given in the original study.

\[ pH = 7 - \log(H) \]

*Equation 6.6: Conversion of hydrogen ions to pH*

The lansoprazole PKPD model parameter values are taken from [257] and are provided in Table 6.4. The group 1 patient data were used. As no BSV values were reported in the analysis the value of BSV was set to 30% for each PKPD parameter. As mentioned in the atorvastatin case, residual variability was not incorporated here since the goal was to determine successful attainment of the true effect for each patient rather than an observed effect.

**Table 6.4: Lansoprazole PKPD model parameters**

<table>
<thead>
<tr>
<th>PKPD model parameter</th>
<th>Parameter estimate</th>
<th>BSV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (L)</td>
<td>42.8</td>
<td>30%</td>
</tr>
<tr>
<td>k (/h)</td>
<td>0.28</td>
<td>30%</td>
</tr>
<tr>
<td>t_{lag} (h)</td>
<td>0.49</td>
<td>30%</td>
</tr>
<tr>
<td>k_{deg} (/h)</td>
<td>0.04</td>
<td>30%</td>
</tr>
<tr>
<td>k_{d} (/μg.L⁻/h)</td>
<td>0.13</td>
<td>30%</td>
</tr>
<tr>
<td>k_{m} (mM)</td>
<td>26.6</td>
<td>30%</td>
</tr>
<tr>
<td>k_{out} (/h)</td>
<td>0.59</td>
<td>30%</td>
</tr>
</tbody>
</table>

*V = volume of distribution of central compartment, k = elimination rate constant, t_{lag} = absorption lag time, k_{d} = first elimination rate constant of proton pumps, k_{deg} = second elimination rate constant of proton pumps, k_{m} = mean acid production rate, which was set to R_{init}, k_{out} = elimination rate constant of gastric acid. Bioavailability was assumed to be 1.*

* *A BSV value of 30% was chosen arbitrarily.*

PKPD parameters of the lansoprazole PKPD model were used for omeprazole and no adaptation was made to the model.

Similar to atorvastatin, two scenarios were considered (1) perfect adherence and (2) imperfect adherence.
The dose of omeprazole prescribed for each patient was:
1) Patient 3: 20 mg
2) Patient 4: 20 mg
3) Patient 6: 20 mg
4) Patient 8: 40 mg
5) Patient 21: 20 mg
All patients, apart from Patient 3, were prescribed once daily for 90 days (for this medication refill). Patient 3 was prescribed once daily for 60 days.

6.3.2.2. Extraction of clinically observed adherence profiles

In Chapter 4, there were five patients prescribed omeprazole (Patients 3, 4, 6, 8 and 21). Each clinically observed adherence profile is depicted as follows (Figures 6.6, 6.7, 6.8, 6.9 and 6.10, respectively):

**Figure 6.6:** Clinically observed adherence profile of Patient 3

**Figure 6.7:** Clinically observed adherence profile of Patient 4
The number of random missed doses and drug holidays over the treatment period of 90 days for each patient, and 60 days for Patient 3, is summarised in Table 6.5.

The number of random missed doses observed for Patient 21 was around the mean value of those in Chapter 5 (random missed doses = 13) whereas Patient 4 had twice this value. Patient 4 also had the upper bound of drug holidays in comparison to the drug holiday distribution in Chapter 5.
Table 6.5: Number of missed doses over the 90 treatment day period for each patient prescribed omeprazole

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Random missed doses</th>
<th>Drug holidays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Patient 4</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Patient 6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 21</td>
<td>10</td>
<td>-</td>
</tr>
</tbody>
</table>

6.3.2.3. Parametric simulation of PKPD profiles for each patient

The same methods used for atorvastatin were also used for omeprazole. One thousand sets of individual PKPD parameters were simulated under these 2 scenarios: (1) a perfect adherence profile with the prescribed dose and (2) each observed imperfect adherence profile with the corresponding prescribed dose for each patient. $P_p$ and $P_{ip}$ for each patient were calculated. RF for each patient was then determined.

6.3.2.4. Qualification of attainment of a treatment target

The assumption was the same as that for atorvastatin to ensure that steady state was achieved in all scenarios. The time to steady state was assumed to be 20 days. Therefore, the first 20 days were discarded and not included in determination of RF. Successful attainment of a treatment target was considered as time above the therapeutic criterion. The therapeutic criterion was defined as a pH of 4, which is a recommended treatment target for GORD [259]. Successful treatment was defined as where at least 60% of steady state trough values were above the therapeutic pH criterion.

6.3.2.5. Visualisation of the time course of drug effect profile

To visualise the time course of drug effect, the pH vs time profile for an average patient with mean population parameter estimates was simulated under each observed imperfect adherence as well as perfect adherence at each prescribed dose.
6.4. Results

6.4.1. Atorvastatin

6.4.1.1. Relative forgiveness for each patient prescribed atorvastatin

Table 6.6: Relative forgiveness for each patient prescribed atorvastatin

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Prescribed dose</th>
<th>( P_p^* )</th>
<th>( P_{ip}^* )</th>
<th>RF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 17</td>
<td>40 mg</td>
<td>0.527</td>
<td>0.494</td>
<td>0.88</td>
</tr>
<tr>
<td>Patient 19</td>
<td>80 mg</td>
<td>0.578</td>
<td>0.537</td>
<td>0.85</td>
</tr>
<tr>
<td>Patient 23</td>
<td>10 mg</td>
<td>0.407</td>
<td>0.380</td>
<td>0.89</td>
</tr>
</tbody>
</table>

* \( P_p^* = \) The probability of successful attainment of a treatment target under perfect adherence
* \( P_{ip}^* = \) The probability of successful attainment of a treatment target under imperfect adherence
* RF* = Relative forgiveness

Based on these findings, atorvastatin is forgiving for all these three patients under scenarios that actual random missed doses over the 90 treatment day period were 12, 4 and 2 doses in Patients 17, 19 and 23, respectively. Only Patient 17 had drug holidays (on one occasion).

The RF results indicated that overall, success was around 10-15% less likely with atorvastatin for imperfect adherence given the actual adherence profile observed in each patient. The findings also showed that the \( P_p \) value was particularly low for Patient 23 (\( P_p = 0.407 \)), this may be due to the relatively low given dose of 10 mg.
6.4.1.2. Visualisation of an average patient with mean population parameter estimates for the time course of LDL

Figures 6.11 to 6.13 show the LDL vs time profile for an average patient with mean population parameter estimates simulated under each observed imperfect adherence as well as perfect adherence at each prescribed dose.

1) Patient 17 scenario

Figure 6.11: The time course of LDL of an average patient prescribed atorvastatin 40 mg with perfect adherence (left panel) and Patient 17’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success.
2) Patient 19 scenario

Figure 6.12: The time course of LDL of an average patient prescribed atorvastatin 80 mg with perfect adherence (left panel) and Patient 19’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of LDL<2.6 mmol/L.
3) Patient 23 scenario

**Figure 6.13:** The time course of LDL of an average patient prescribed atorvastatin 10 mg with perfect adherence (left panel) and Patient 23’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of LDL<2.6 mmol/L.
6.4.2. Omeprazole

6.4.2.1. Relative forgiveness for each patient prescribed omeprazole

Table 6.7: Relative forgiveness for each patient prescribed omeprazole

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Prescribed dose</th>
<th>( P_p^* )</th>
<th>( P_{ip}^* )</th>
<th>RF #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 3</td>
<td>20 mg</td>
<td>0.49</td>
<td>0.481</td>
<td>0.96</td>
</tr>
<tr>
<td>Patient 4</td>
<td>20 mg</td>
<td>0.451</td>
<td>0.056</td>
<td>0.07</td>
</tr>
<tr>
<td>Patient 6</td>
<td>20 mg</td>
<td>0.486</td>
<td>0.489</td>
<td>1.01</td>
</tr>
<tr>
<td>Patient 8</td>
<td>40 mg</td>
<td>0.646</td>
<td>0.621</td>
<td>0.90</td>
</tr>
<tr>
<td>Patient 21</td>
<td>20 mg</td>
<td>0.489</td>
<td>0.481</td>
<td>0.97</td>
</tr>
</tbody>
</table>

\( P_p^* = \text{The probability of successful attainment of a treatment target under perfect adherence} \)

\( P_{ip}^* = \text{The probability of successful attainment of a treatment target under imperfect adherence} \)

\( RF # = \text{Relative forgiveness} \)

Based on these findings, omeprazole appeared forgiving for Patients 3, 6, 8 and 21. However, it was not forgiving for Patient 4. The reason for this is the less erratic adherence profiles of Patients 3, 6 and 8. Notably Patent 3 had only 2 random missed doses and Patients 6 and 8 had no random missed doses whereas Patient 21 had more random missed doses (10 doses). These four patients had no drug holidays. In contrast, Patient 4 had an extremely erratic adherence profile with 25 random missed doses and 3 drug holidays over the 90 treatment day period.

The results suggested the predominant influence of each individual adherence profile on RF. Omeprazole is forgiving when patients are to a great extent adherent (Patients 3, 6 and 8) or moderately imperfectly adherent (Patient 21) whereas it is not forgiving when patients are considerably imperfectly adherent (Patient 4).
6.4.2.2. Visualisation of an average patient with mean population parameter estimates for the time course of pH

Figures 6.14 to 6.18 show the pH vs time profile for an average patient with mean population parameter estimates simulated under each observed imperfect adherence as well as perfect adherence at each prescribed dose.

1) Patient 3 scenario

![Graph showing pH vs time for perfect adherence and Patient 3's adherence profile.](image)

**Figure 6.14:** The time course of pH of an average patient prescribed omeprazole 20 mg with perfect adherence (left panel) and Patient 3’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of pH>4.
2) Patient 4 scenario

![Graphs showing pH over time for an average patient and Patient 4's adherence profile.](image)

**Figure 6.15:** The time course of pH of an average patient prescribed omeprazole 20 mg with perfect adherence (left panel) and Patient 4’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of pH>4.
3) Patient 6 scenario

![Graphs showing pH time course for average patient and Patient 6's adherence profile](image)

**Figure 6.16:** The time course of pH of an average patient prescribed omeprazole 20 mg with perfect adherence (left panel) and Patient 6’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of pH>4.
4) Patient 8 scenario

**Figure 6.17:** The time course of pH of an average patient prescribed omeprazole 40 mg with perfect adherence (left panel) and Patient 8’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of pH > 4.
5) Patient 21 scenario

Figure 6.18: The time course of pH of an average patient prescribed omeprazole 20 mg with perfect adherence (left panel) and Patient 21’s adherence profile (right panel) with the top row depicting the adherence profile. The red line is the threshold of a target success of pH > 4.
6.5. Discussion

This study has applied the relative forgiveness criterion developed in Chapter 5 to other therapeutic agents, namely atorvastatin and omeprazole and to actual adherence profiles for individual patients. This study evaluates whether the proposed RF criterion is generalisable to evaluation of other drugs of interest and its value at an individual patient level.

For illustrative purposes in this work, a possible classification of forgiveness could be as per Table 6.8.

<table>
<thead>
<tr>
<th>Degree of forgiveness</th>
<th>RF value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgiving</td>
<td>&gt; 0.7</td>
</tr>
<tr>
<td>Moderately forgiving</td>
<td>0.5-0.7</td>
</tr>
<tr>
<td>Not forgiving</td>
<td>&lt; 0.5</td>
</tr>
</tbody>
</table>

For atorvastatin RF, the therapeutic criterion was chosen to be an LDL concentration of 2.6 mmol/L and therapeutic success defined when at least 60% of a dosing profile achieved LDL values below that criterion. The RF value for each patient, under their own adherence profile, was found to be 0.88, 0.85 and 0.89 for Patients 17, 19 and 23, respectively. Atorvastatin appears forgiving, given that RF values were more than 0.7 across all patients. This finding is not surprising and can be explained based on the PK and PD properties of atorvastatin. PK: Atorvastatin is a parent drug and its metabolite is atorvastatin lactone. The half-life of atorvastatin parent in the central compartment is close to 20-30 hours given its interconversion with its metabolite. PD: Atorvastatin inhibits HMG-CoA reductase enzyme thereby cholesterol synthesis is inhibited and the turnover of cholesterol is determined by its half-life of the order of 3-4 days [134]. PKPD: Hence, the duration of effect lasts longer than the once daily dosing interval. Although 12 random missed doses occurred with Patient 17 over the 90 day treatment period, this impact of random missed doses was unlikely to diminish RF substantially. Further to atorvastatin PKPD properties, in this
group of patients, another factor that may attribute to atorvastatin being forgiving could be that observed imperfect adherence patterns did not deviate to a large extent from perfect adherence. For timing variability, the timing distribution of all the three patients did not markedly departure from each patient’s nominal timing of taking drugs. No drug holidays were observed for Patients 19 and 23 and one drug holiday was observed for Patient 17.

A prior atorvastatin simulation study also suggested that the “forgiveness” (this forgiveness was not based on an explicit classification as described here) property of atorvastatin allowed for certain events of random missed doses or drug holidays, but not for early discontinuation [231]. This study simulated patterns of missed doses based on previous dose taking behaviour [231]. There have been several studies investigating the effect of alternate day dosing statins, including atorvastatin, on LDL reduction in comparison to once daily dosing statins, which was recently reviewed by Marcus et al. [260]. Although the study of Jafari et al. [261] found insignificant LDL reduction between the alternate day and once daily dosing atorvastatin, some studies found the significant results. Given that the duration of statin effect is depended upon the turnover of cholesterol, therapeutic success should be attained irrespective of morning or evening dosing. This is supported by a simvastatin simulation study with a range of doses that LDL reduction percentages were similar between evening dosing (33-43%) and morning dosing (31-43%) [132]. This finding may assist patients in clinical settings since the study of Vrijens et al. found that patients prescribed morning dosing were more likely to take doses correctly than those prescribed with evening dosing (odds ratio=1.38, CI=[1.36, 1.41]) [56].

It has been established that apart from statin cholesterol lowering properties, statins may have a pleiotropic effects, which are thought to be independent of plasma cholesterol concentration [262]. This includes improving endothelial dysfunction by increasing endothelial nitric oxide production; increasing atherosclerotic plaque stability to prevent plaque rupture by decreasing macrophage cholesterol accumulation; reducing vascular oxidative stress and inflammation as well as thrombogenic response [262]. In addition, the
influence of the time course of LDL on coronary vessels is unknown. It is possible that these effects could have a longer time frame of turnover than plasma cholesterol and hence statins could be considerably more forgiving than illustrated here.

Several studies have reported non-adherence with respect to early discontinuation of the use of statins [252, 263-265]. The discontinuation rate over time varied from study to study. In the following studies, it was found that the discontinuation rate was around 50% after 6 months to 1 year [263-265]. Limited studies have investigated the implementation phase e.g. [266]. Hence, it is important to emphasise that although atorvastatin is forgiving patients still require to persist with taking drugs to be able to gain benefits. This was also highlighted in the atorvastatin simulation study [231] where by 6 months, 58.2% of patients persisting with the treatment exhibited LDL reduction of 49.5% (95%CI, 30.5%-65.1%). In contrast, LDL reduction of 1% (95%CI, 0%-3.9%) was observed in 41.8% of patients discontinuing the treatment [231].

For atorvastatin $P_p$, our findings showed that $P_p$ was around 0.5-0.6 for Patient 17 (atorvastatin 40 mg) and Patient 19 (atorvastatin 80 mg) whereas $P_p$ was around 0.4 for Patient 23 (atorvastatin 10 mg). It can be seen that the RFs were greater with the higher doses. Although the atorvastatin RF values suggested that there was little difference in attaining the LDL target success between observed imperfect adherence and perfect adherence, it should be noted that LDL monitoring may be required in around 50% of the population to maintain the treatment success (i.e. $P_p$ values that meet pre-defined targets).

For omeprazole RF, the therapeutic criterion was chosen to be a pH value of 4 and therapeutic success defined when at least 60% of a dosing profile achieved pH values above that criterion. An RF value of each patient, under their own adherence profile, was found to be 0.96, 0.07, 1.01, 0.90 and 0.97 for Patients 3, 4, 6, 8 and 21, respectively. Our findings suggested that whether or not omeprazole is forgiving depends substantially on each individual adherence profile in conjunction with omeprazole PKPD properties. This means that omeprazole is likely not to be a forgiving drug across the population since
changes in adherence patterns result in wide variability in RF values. However, and interesting, patients taking omeprazole may be, on the whole, more adherent and hence RF values may be good. Specifically, in these 5 patients, it may be concluded that imperfect adherence patterns may be categorised into 3 groups as (1) close to perfect adherence where mostly timing variability occurred with none or only 1-2 random missed doses over the treatment period (Patients 3, 6, 8) (2) moderately imperfect adherence (see Patient 21’s adherence profile) and (3) extremely imperfect adherence (see Patient 4’s adherence profile). For Patient 21, the patient’s individual adherence profile may be at the cusp where the PKPD properties of omeprazole could compensate and hence resulted in an RF value of 0.97. Whereas for Patient 4 omeprazole would provide poor symptom/pH control. As discussed in Chapter 4 MEMS feasibility study that patients’ disease information was not accessible to us. Given the long term nature of treatment, it is plausible that omeprazole was prescribed for these patients for the treatment of chronic GORD.

Although it may be perceived that omeprazole is likely to be forgiving due to its covalent binding of active forms, sulfenamide to cysteine at the proton pump, possible reasons explaining our findings could be that the recovery of acid secretion is based on binding sites of sulfenamide and cysteine i.e. cysteine locations [258, 267, 268] in addition to de novo synthesis of proton pumps [258]. It has been suggested that cysteine 813 is a common binding site for all PPIs, in addition to this, each PPI has the selectivity binding with other cysteines as shown in Table 6.9 [258, 267-269].
Table 6.9: Cysteine binding site that each PPI binds in addition to cysteine 813 [258, 267-269]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cysteine binding site</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Cysteine 892</td>
<td>Luminal surface of proton pumps</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Cysteine 892</td>
<td>Luminal surface of proton pumps</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Cysteine 321</td>
<td>Luminal surface of proton pumps</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Cysteine 822</td>
<td>Deeper within the membrane domain of proton pumps</td>
</tr>
<tr>
<td>Tenatoprazole</td>
<td>Cysteine 822</td>
<td>Deeper within the membrane domain of proton pumps</td>
</tr>
</tbody>
</table>

The disulfide bond between sulfenamide and cysteine can be cleaved by reducing agents, e.g. glutathione [241]. In parietal cells, there are 2-3 mM of the reducing agent of glutathione [241]. Given that cysteine 822 is located deeper within the membrane domain of proton pumps, glutathione is inaccessible to this cysteine binding site [258]. A three dimensional structure of the proton pump with different locations of cysteine binding sites is shown in Figure 6.19. Hence, the duration of effect of pantoprazole and tenatoprazole may depend on de novo synthesis of proton pumps solely whereas that of other PPIs may depend on both de novo synthesis of proton pumps and reversal of the covalent disulfide bond [258, 267, 268]. The turnover of proton pumps was suggested to be around 54 hours [267]. Pantoprazole and tenatoprazole might therefore appear to be more forgiving in comparison to omeprazole and lansoprazole. The half-life of PPIs is short in comparison to their once daily dosing interval i.e. around 1-2 hours. Therefore, their prolonged duration is given by their PD properties. However, this prolonged duration lasts shorter than or approximately 1 day for lansoprazole and omeprazole. It was suggested that half-life of recovery of acid secretion of lansoprazole, omeprazole and pantoprazole in human is around 15, 28 and 46 hours, respectively [258, 270, 271].
For omeprazole $P_p$, the findings showed that $P_p$ was around 0.5 for all the 4 patients with omeprazole 20 mg. $P_p$ was around 0.6 for Patient 8 (omeprazole 40 mg). Given that GORD is a symptomatic disease, it may be expected that a patients’ symptoms may have a negative reinforcement effect and thereby enhance adherence, which perhaps could be seen in Patients 3, 6, 8 whose adherence profiles were close to perfect. Due to the extremely erratic profile of Patient 4, the reason for this is unknown but it might be the case that this patient may not require omeprazole. Overprescribing PPIs has been reported elsewhere [272-274]. A Patient 4’s adherence profile with the higher dose of omeprazole 40 mg was also simulated. The RF result for this was 0.031 ($P_p = 0.632$ and $P_{ip} = 0.051$) indicating that the adherence profile was so poor that the higher dose prescribed could not compensate. Our findings of the $P_p$ values suggested that around 50% appropriately prescribed omeprazole i.e. require omeprazole, the

**Figure 6.19:** Three dimensional structure of the proton pump with different locations of cysteine binding sites. Cysteine is denoted as C. The Figure depicts the location of cysteine 321, 813, 822 and 892. A transmembrane segment 8 is split to show the location of cysteine 822 which is inaccessible to glutathione. Reused with permission from Elsevier Limited, Gastroenterology 123: 1588-97, copyright 2002 [256].
negative reinforcement of experiencing symptoms resulting in taking doses should act as a tool of monitoring pH to maintain the treatment success. For example, dose adjustment may be needed when patients provide feedback about uncontrolled symptoms.

It should be noted that as this study used actual adherence patterns which depends on each individual observed profile, the purpose of this current work was to provide RF for each individual patient. Therefore, the extent of RF could differ from patient to patient especially when the component of adherence patterns differ to a great extent. Secondly, given that there were no specific population PKPD models for both atorvastatin and omeprazole, it could be expected that there may be more variability around model parameter estimates. Thirdly, the evaluation of classification for forgiveness is warranted for future work to determine appropriateness of the values and their generalisability to other drugs. Finally, interpretation should be made with caution when RF is used at the individual level in terms of adherence patterns as seen in the omeprazole case. Ultimately, whether or not a drug is forgiving for each patient depends on the individual adherence profile in conjunction with the individual PKPD properties.

6.6. Conclusions

In conclusion, this study shows that relative forgiveness is generalisable to other drugs of interest. In addition, relative forgiveness can be computed at the individual level given each individual patient’s adherence patterns. This study illustrates the implication of relative forgiveness for clinical practice.
Chapter 7: Discussion and future prospects
Chapter 7: Discussion and future prospects

7.1. Synopsis of this thesis

This thesis aimed to quantify adherence, the influence of factors on adherence and the influence of adherence on therapeutic outcomes. This involved a series of investigations. In Chapter 2, the independent influence of various factors, namely disease, age and dosing regimens on adherence in two different diseases was determined. Appropriate measures of adherence in relation to adherence patterns were explored in Chapter 3. The work included an investigation of measures of adherence used in the Medication Event Monitoring System (MEMS) literature. The feasibility of conducting the first MEMS study in New Zealand was undertaken in Chapter 4. In this chapter, adherence pattern data were also presented. In Chapter 5, a criterion to quantify forgiveness of drugs to imperfect adherence was proposed. Illustration and evaluation of the developed criterion, using a theoretical example and an actual drug, respectively, were also conducted. This led to an application of the forgiveness criterion to other drugs of interest using an individual patient’s clinically observed adherence profile (from Chapter 4) in Chapter 6.

7.2. Discussion of the findings

7.2.1. A model-based meta-analysis of the influence of factors that impact on adherence

Factors influencing adherence have been previously investigated [12, 30, 31]. However, the model-based meta-analysis (MBMA) technique adopted in Chapter 2 has added further information which could not be teased out via traditional meta-analyses. That is, this MBMA technique allows for continuous dependent variables e.g. percentage of doses taken per day or more accurate adherence data where they are available. This application shares a similar concept with previous research where drug response longitudinal data were employed [137, 138, 275, 276]. The use of continuous dependent variables can provide a deeper insight into the influence of factors on adherence compared to the use of traditional binary data i.e. an event happens or not/success or failure.
Additionally, the MBMA technique allows for multivariate analyses. Therefore, various factors of interest can be concurrently considered resulting in adjusted effects, i.e. multivariate models, in addition to combined effects obtained from univariate models.

In Chapter 2, factors influencing adherence that were investigated included disease, age and dosing regimen. Although there were also other factors of interest including duration of treatment, medication class and pill burden, these factors could not be considered due to infrequent reporting across studies. It is noted that our analysis considered a ‘subset’ of factors in the five dimensions, i.e. (1) socioeconomic related factors, (2) healthcare team and system related factors, (3) condition related factors, (4) therapy related factors and (5) patient related factors [12, 31]. That is, disease, age, and dosing regimens are categorised into dimensions (3), (5) and (4), respectively. However, it was unlikely to be able to account for factors much more globally in this MBMA manner given that most of primary studies were not designed for this research question.

The findings of the influence of disease, age and dosing regimen on adherence from this work were: (1) although the influence of disease on adherence was significant, it is likely to be of limited clinical significance (2) increased age positively impacts on adherence and (3) the greater frequency of dosing regimens negatively impacts on adherence. Here, some recently updated findings on factors influencing adherence, from a review of 51 systematic reviews of Kardas et al. in 2013 [31], are provided for a comparison with our findings. The influence of patient characteristics on adherence appeared inconsistent. With respect to age, corresponding findings that older people were better adherent was reported. However, some studies found that age had no significant impact on adherence. It has also been found that females seemed to be more adherent than males with insignificant influence reported in some studies [31]. Being married and higher education appeared to have positive impact on adherence [31]. With regards to disease, it was suggested that patient motivation to adhere to prescribed medications decreased when the disease was asymptomatic or clinical improvement was observed. In contrast, increased
disease severity was found to positively influence adherence [31]. The asymptomatic/symptomatic aspect on adherence was also explored in Chapter 6 with the two comparison groups prescribed atorvastatin and omeprazole. The majority of studies with respect to the frequency of dosing regimens in this review also reported corresponding findings [31].

Although our findings in this MBMA work should be treated as exploratory, it is recommended that pharmacist adherence support services should also target the younger who may be less adherent given that most of the services are specifically targeted patients aged ≥ 65 years. It is also worth noting that in some circumstances, prescribing a higher frequency of dosing regimens may actually benefit patients e.g. twice daily compared to once daily dosing [238]. This could be explained as the probability of missing two consecutive missed doses with once daily dosing was reported to be twice as high as that observed with twice daily dosing [238]. Given that a once daily dosing drug is normally perceived most superior in terms of enhanced adherence, it is important to emphasise that ultimately, the proportion of time that patients attain their treatment target should be considered. Hence, it has been suggested that twice daily dosing is more forgiving [109, 232, 238].

7.2.2. Measures of adherence in the MEMS literature

The context to conduct this work of measures of adherence in the MEMS literature in Chapter 3 arose from the intention of considering more informative adherence data as a dependent variable in the MBMA work in Chapter 2.

The findings in Chapter 3 demonstrated that various adherence measures were used in a subset of MEMS literature with respect to HIV and hypertension therapeutic areas with different frequency of the use of each measure. The adherence measures included percentage of doses taken, percentage of doses taken on schedule, percentage of days with correct doses taken, percentage of days with correct dosing and percentage of consecutive missed doses. It was found that the global measure i.e. percentage of doses taken, was the most commonly used measure despite the advanced ability of MEMS devices to
record patterns of drug taking. Figure 7.1 illustrates the limitation of this measure. Four hypothetical examples with a once daily dosing drug are depicted. Each profile has the same percentage of doses taken = 75% over the treatment period of 60 days. It shows that despite the same percentage of doses taken, four different adherence patterns are seen: example 1, random missed doses occur with no drug holidays; example 2, two consecutive drug holidays occur at the beginning of the treatment; example 3, one drug holiday occurs at the end of the treatment with some random missed doses over the period; and example 4, two drug holidays occur over the period. This figure reiterates that information of adherence patterns, which is crucial for understanding the time course of drug effects, cannot be captured using percentage of doses taken (pill count) information.

Percentage of days with ‘correct dosing’ appears to be the most informative summary adherence measure. ‘Correct dosing’ means correct number of doses taken as well as correct timing. Correct timing is defined as: 1) an interval of 6 hours sooner or later than the mode of timing of doses taken for once daily dosing and 2) for twice daily dosing, an interval of 3 hours sooner or later than the mode of timing of doses taken, for morning doses and evening doses. This measure covers percentage of too short or too long dosing intervals. In other words, it accounts for percentage of doses taken per schedule of each dose during the day. In addition, a missed dose component, including random missed doses and drug holidays, is considered. However, based on the findings from Chapter 5 that the influence of timing variability on therapeutic success is probably of minimal concern, percentage of days with correct doses may be a sufficiently informative adherence measure in this circumstance.
Figure 7.1: Four hypothetical examples with a once daily dosing drug. All four profiles have the same percentage of doses taken = 75%. The treatment period is 60 days.
To obtain further information regarding the number as well as the occurrence of missed doses, a particular timeframe should be employed. A one month and three month timeframe for random missed doses and drug holidays, respectively was initially suggested. However, these timeframes may be revised in future studies based on observed adherence patterns. To complete the entire picture of adherence process, implementation should be considered in conjunction with initiation and discontinuation.

7.2.3. A MEMS feasibility study in New Zealand

In Chapter 4, two main components were undertaken. Firstly, the feasibility of conducting the first MEMS study in New Zealand, with respect to (1) identification of patients (2) recruitment and (3) retention and patient acceptability, was investigated. Secondly, given the collected data, patterns of adherence were explored using appropriate adherence measures suggested in Chapter 3. The proposed “rule of sixes” was then evaluated.

For the first part, the MEMS feasibility study, it was found that the pharmacists’ perspectives was a contributing factor to identification of patients. For example, they suggested to exclude patients prescribed with a perceived high risk drug like warfarin. Specified disease areas or drug classes appeared to decrease the recruitment rate, which is important to consider when conducting a larger study. Another factor affecting the recruitment rate was the proportion of patients choosing not to participate in the study. The finding suggested that a medication tray was a preferred option in some patients. Based on patients’ response to questionnaires, overall, patients found using MEMS was easy/very easy, practical/very practical and comfortable/very comfortable. With regards to MEMS affecting a patients’ medication taking behaviour, not surprisingly, one of the reasons for this was becoming more adherent due to the perception of being monitored. However, three quarters of patients reported that in their opinion MEMS devices did not affect their medication taking behaviour. Information about the proportion of patients willing to use MEMS for another prescription is useful for a future study with a longer duration of treatment (in
this study: 76% of patients). The retention rate, which was found to be 86% in this study, allows for the estimation of extra recruitment.

For the second part, patterns of adherence, obtained adherence data were summarised. The summarised adherence patterns were then used to evaluate the rule of sixes. It was found that medication taking behaviour in this group of patients did not follow the rule of sixes. Observed adherence patterns were therefore reported using our developed criterion, which comprises 6 items as follows: (the proportion of patients exhibiting as per each item is presented)

1. takes all prescribed doses but timing is fairly inconsistent (3/25)
2. has 90% to less than 100% of days with correct dosing (13/25)
3. has 80% to 90% of days with correct dosing (5/25)
4. has 55% to 75% of days with correct dosing (4/25)
5. has 1 to 5 random missed doses for 1st, 2nd, and 3rd month (5/22)
6. has 1 drug holiday per 3 months (4/22)

For items 5 and 6, patients prescribed with a monitoring period less than 3 months were excluded.

In addition, as recognised that some researchers used, for example, “80% of percentage of doses taken” as a cut-off to define “good adherence”, our criterion illustrates the use of a clear and informative cut-off of percentage of days with correct dosing.

7.2.4. Quantification of the forgiveness of drugs to imperfect adherence

It has been recognised that non-adherence can occur at various stages of adherence process. These include failure to initiate, suboptimal implementation and early discontinuation. As a consequence, there have been many attempts to explore interventions to improve adherence [33, 34, 36, 42]. Findings arising from intervention research have been inconclusive. Ultimately, to enhance the effectiveness of interventions, it has been proposed that interventions should be designed more systematically i.e. multi-level interventions. These comprise patient level, provider level, organisation of care processes level; and health care system level [32, 48].
The study conducted in Chapter 5 has looked at an alternative where the intention was not to improve adherence but to ‘compensate’ for poor adherence with respect to suboptimal implementation. This approach lies in the choice of forgiving drugs. According to the notable quote “Drugs don’t work in patients who don’t take them.”, the importance of being adherent to attain therapeutic success has been highlighted. Given that forgiveness is a drug specific property that determines how sensitive therapeutic success is under imperfect adherence, forgiving drugs may work sufficiently in patients who occasionally miss doses.

Based on the proposed concept of forgiveness as $F = D - I$ [57] where $F =$ forgiveness, $D =$ duration of action, $I =$ dosing interval, it is seen that the way forward to better understand the forgiveness property of drugs is to ‘quantify’ forgiveness. That is, pharmacokinetic-pharmacodynamic (PKPD) variability and adherence variability are essential components to be considered. Hence, in Chapter 5, a criterion to quantify forgiveness was developed. The criterion is described as relative forgiveness (RF). RF considers the probability of therapeutic success given imperfect adherence ($P_{ip}$) and the probability of therapeutic success given perfect adherence ($P_p$), and subsequently yields the number of times more likely that target success is attained under perfect adherence compared to imperfect adherence.

Here, note that the relationship between $P_p$ and $P_{ip}$ is of importance. $1 - P_p$ quantifies the proportion of patients in the population who do not achieve therapeutic success although they are perfectly adherent. This emphasises the potential requirement of treatment monitoring for each individual patient to ensure the successful attainment of a target. Figure 7.2 depicts the comparison of the time course of drug effect of two individuals under perfect adherence condition where the left panel is an average patient with mean population parameter estimates (patient A); and the right panel is a patient with the same parameter values as patient A, apart from twice clearance (patient B). Under the same treatment as patient A, therapeutic success is not achieved in patient B.
Figure 7.2: Illustration of two individuals who are perfectly adherent. The left panel is an average patient A with mean population parameter estimates. The right panel is a patient B with the same parameter values as patient A, apart from twice clearance. The first row is a perfect adherent MEMS profile. The second row is a PK profile. The third row is a PKPD profile. The red line is a hypothetical threshold of a target success (above the line denotes success).

Given the same interpretation of RF as a familiar odds ratio, RF therefore covers the quantification of forgiveness in two scenarios, namely (1) forgiveness of a given drug; and (2) forgiveness between two drugs whose effects can be quantified on the same biomarker of response.

For the purpose of the illustration of RF, a simple theoretical PKPD model was chosen. The illustration of RF provided two main implications with respect to both clinical practice and drug development as follows: (1) in this example, the influence of only missed doses (random missed doses + drug holidays) was stronger than that of only timing variability; and (2) theoretical modification to the properties of an original drug e.g. twice the half-life as well as twice the potency resulted in enhanced forgiveness property (RF>1) despite the presence of imperfect adherence.

The application of RF with a published warfarin population kinetic pharmacodynamic model [229] suggested that warfarin is a relatively forgiving drug (RF=0.78). However, it is crucial to monitor a patient’s International Normalised Ratio (INR) in around 40% of the population for successful attainment of a treatment target (PP=0.58), based on a liberal INR target range of 2-3.5.
7.2.5. Application of relative forgiveness using clinically observed adherence profiles

The important implication of relative forgiveness for clinical practice was demonstrated in Chapter 6. In this chapter, it was found that RF was generalisable to evaluation of other drugs of interest. Additionally, it can be used at an individual patient level in terms of each patient’s clinically observed adherence profile.

Actual patients’ adherence data and dosing for atorvastatin (n=3) and omeprazole (n=5) were obtained from Chapter 4.

Overall, the findings of both atorvastatin and omeprazole emphasise that when determining whether a drug is forgiving for each patient, it is important to consider both two components: (1) the individual adherence profile and (2) the individual PKPD properties.

For atorvastatin RF, atorvastatin appears forgiving with RF values greater than 0.7 across all three patients. This finding may be explained based on (1) the PKPD properties of atorvastatin with a long half-life and the turnover of cholesterol being determined by the half-life of cholesterol and (2) individual adherence profiles (The observed random missed doses and drug holidays for Patients 17, 19 and 23 were 12, 4 and 2; and 0, 0, and 1, respectively). In general the profiles did not substantially deviate from perfect adherence. Where 12 random missed doses occurred, atorvastatin PKPD properties of the duration of drug effect being longer than the once daily dosing interval could compensate.

For omeprazole RF, omeprazole seems forgiving when patients are close to perfect adherence and not forgiving when patients are extremely poorly adherent. Therefore, on the whole, omeprazole is likely not to be a forgiving drug across the population. The observed random missed doses and drug holidays for Patients 3, 4, 6, 8 and 21 were 2, 25, 0, 0 and 10; and 0, 3, 0, 0 and 0, respectively. The great variety of adherence patterns driven by Patient 4 predominates wide variability of RF values.

As noted that RF is interpreted based on the relationship between $P_p$ and $P_{ip}$, RF values may be close to one despite values of $P_p$ close to zero. This chapter...
also demonstrated the importance and interpretation of \( P_p \) with representative drugs used for prevention of disease i.e. atorvastatin and for treatment of symptomatic disease i.e. omeprazole.

For atorvastatin \( P_p \), \( P_p \) values of around 0.4-0.6 suggested the need to monitor low-density lipoprotein (LDL) in around 50% of the population to maintain the attainment of a LDL target.

For omeprazole \( P_p \), close to perfect adherence (e.g. no or a few missed doses; and timing variability was within an interval of 6 hours sooner or later than the mode of timing of doses taken) observed in patients may be due to uncontrolled acid reflux reinforcing patients’ adherence to be consistently close to perfect. \( P_p \) values of around 0.5 suggested that a pH target may not be achieved in around 50% of the population. These findings implied that in patients who require omeprazole for long term treatment, negative reinforcement of uncontrolled symptoms can provide feedback to a clinician to adjust the dose to maintain therapeutic success. When negative reinforcement from patients does not happen, it may be implied that those patients do not require omeprazole.

7.3. Future prospects

7.3.1. Measures of adherence and a MBMA of the influence of factors that impact on adherence

Here, considering adherence meta-analyses in general first, it has been shown that several previous meta-analyses [14-17] included studies with a variety of methods to monitor adherence. These methods included self-reporting, pill counts, prescription refill records and electronic monitoring. This led to inconsistent measures of adherence e.g. good adherence was defined as adherence \( \geq 80\% \) of adherence results obtained from an individual method. Hence, two implications for future adherence work are reflected: (1) the electronic monitoring method e.g. MEMS should be considered and (2) patterns of adherence recorded by MEMS rather than sole percentage of prescribed doses taken data should be reported.
As previously discussed, patterns of adherence can be summarised in various ways. To be consistent in future studies, it is suggested that percentage of days with correct dosing could be the primary adherence measure of use. Studies should also distinguish the three components of adherence: initiation, implementation and discontinuation; and report data as an entire adherence process. Where not possible, studies should at least identify which component of adherence is being addressed e.g. only implementation. If a cut-off of defined adherence is to be used, it should be informative in relation to adherence patterns and clearly explained.

To provide higher level of evidence of this MBMA work, apart from using percentage of days with correct dosing as a dependent variable, it is encouraged that future studies should be designed more appropriately. That is, useful explanatory variable data should be collected and consistently reported in each study. These include age (patient related factors), dosing regimen (therapy related factors), pill burden (therapy related factors) and duration of treatment (condition related factors) to avoid data imputation and to better estimate an adjusted effect of each factor when additional factors are taken into account. In addition, individual patient level data should be provided to allow for the consideration of actual responses, which results in closer to the true influence of various factors.

More broadly, as noted that factors influencing adherence may be extensive, future research may also aim at collecting data in other dimensions e.g. socioeconomic; and healthcare team and system related factors. This will ultimately enable the independent influence of various factors arising from various dimensions to be explored.

7.3.2. A MEMS feasibility study in New Zealand

There are some suggestions for future MEMS studies undertaken in New Zealand. It is important to identify disease areas/drug classes of interest as well as settings for data collection. Although pharmacists perceived warfarin as a “high risk” drug, warfarin is in fact a forgiving drug and may be considered in
future studies. It should also be noted that diagnosed disease information is not accessible through a community pharmacy setting. Discussion about the possibility of recruiting patients with such a drug class with community pharmacists would be helpful. This information is obtainable via patient history of medication refills on pharmacy database throughout the year. Where it appears that a particular drug class is infrequent for prescription refills, alternative settings may be considered such as recruitment through hospital with general practitioner assistance.

For effective recruitment at a community pharmacy, it is suggested that researchers may collaborate with pharmacists to list potential patients based on pharmacy database and subsequently contact them for study participation. This approach allows most relevant patients to be identified and perhaps results in higher number of patients agreeing to participate. Patients may be more likely to be willing to participate given their established rapport with pharmacists. In addition, recruitment timeframe can be more appropriately estimated based on known prescription refill intervals i.e. 1 month or 3 months. In future studies, where high number of patients refuse to participate due to medication aid preference, it might be worth considering an electronic monitoring designed for poly-medications.

In our study, there was one size of MEMS used to enable most of medications with a 3 month prescription refill to fit in. To increase patient acceptability of the use of MEMS, different sizes of the bottles in relation to the size and the total number of pills per prescription refill may be considered in future studies. This may facilitate patients when travelling in the case that smaller sizes of the bottles can be used.

7.3.3. **Quantification of forgiveness of drugs to imperfect adherence and corresponding applications**

The relative forgiveness criterion can be applied to drugs of interest with their dosing regimens in future work. For instance, a comparison of relative forgiveness of drugs within the same drug class, whose effects can be quantified
on the same biomarker of response, could be investigated. Subsequently, this quantification of forgiveness could be extended to various drug classes. Published population PKPD models could be identified to obtain PKPD parameters. It is suggested that adherence patterns considered for computing relative forgiveness should be specifically related to those observed in studied subpopulations. The appropriate classification of forgiveness could then be determined based on RF values of various drugs within and across drug classes. This work would be of clinical value for the decision of selecting drugs for patients. In addition, the association between adherence patterns and PKPD parameters where PKPD parameters were correlated with patient covariates could be further explored.

It is suggested that pharmaceutical industries should be required to report the RF value and $P_p$ for each drug as a part of the new drug application submission process. This would provide clinicians and regulatory authorities with direct ways to consider how effective a drug will be in clinical practice. In addition, relative forgiveness could be employed in drug design to learn quantitatively the importance of: (1) increasing the potency of drugs. This involves developing the new chemical entity of drugs and (2) prolonging the apparent half-life of drugs. This could be done with changing a formulation of already developed drugs. The latter approach may be preferable since it is likely to be less timing consuming and more cost effective. Ultimately during drug development, it should be considered that all things being equal then a drug with the best relative forgiveness should be considered for marketing. For instance, increasing potency may not be feasible where the mechanism of side effects is in-line with the mechanism of beneficial effects.

Given that the influence of timing variability seems to be less pronounced than that of missed doses, this indicates that patients taking doses at erratic timing is ‘better’ than not taking them at all. In clinical settings where patients’ adherence behaviour may be difficult to change, it might be appropriate from time to time to consider a second line agent that may be more forgiving to the primary agent. That is, a drug with a slightly less than optimal clinical response
but is more forgiving may be chosen over a drug with the best clinical response but is less forgiving.

With respect to drugs used for symptomatic diseases, given that uncontrolled symptoms would act as a tool for symptom monitoring, relatively low RF values would not then be expected. Confusion may arise in patients who do not require drugs for symptomatic treatment resulting who then have low RF values. Hence, patient follow-up would be helpful to ascertain this circumstance.

Ultimately, it is important to note that treatment monitoring is still required for perhaps at least half of the population. Hence, it should be bear in mind that occasionally dose adjustment for each individual patient over the treatment period is needed so that a treatment target can be attained.

7.4. Conclusions

Overall, adherence and its link to therapeutic success were quantified and better understood.

Initially, the independent influence of disease, age and dosing regimen on adherence was determined.

Various measures of adherence were used in the MEMS literature. Percentage of prescribed doses taken was the most commonly used measure, however this measure has significant limitations and should not be used. Appropriate measures of adherence in relation to adherence patterns included percentage of days with correct dosing.

The feasibility of conducting the first MEMS study in New Zealand provided suggestions for future studies. Collected data were presented based on adherence patterns.

A criterion to quantify forgiveness of drugs to imperfect adherence was developed. The relative forgiveness criterion was illustrated with a theoretical example and evaluated with a motivating example, warfarin.

Individual patient adherence patterns of two drugs of interest, atorvastatin and omeprazole, collected in the MEMS feasibility study were used for an
application of the developed relative forgiveness criterion. Relative forgiveness is generalisable to other drugs of interest.
These appendices contain additional material related to the individual thesis chapters.
Appendix 1: Appendix to Chapter 2

This appendix is partially based on the following peer-reviewed publication:

A.1.1. Study assumptions

Table A.1.1: Study assumptions

<table>
<thead>
<tr>
<th>Factor</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number of patients</td>
<td>1.1 If the number of patients that completed the study was not provided (i.e. the number of patients that dropped out was not provided) then the number of patients was set to the number of enrolled patients.</td>
</tr>
<tr>
<td></td>
<td>1.2 If the number of patients that completed the study for each dosing regimen was not provided then the number of patients was set to the number of enrolled patients for each dosing regimen.</td>
</tr>
<tr>
<td></td>
<td>1.3 If either the number of patients that completed the study for each dosing regimen or the number of enrolled patients for each dosing regimen were not provided then the number of enrolled patients was used with the average dosing regimen (e.g. the average dosing regimen for once and twice daily dosing regimens was 1.5) (one study).</td>
</tr>
<tr>
<td></td>
<td>1.4 If either the number of patients that completed the study for each dosing regimen or the number of enrolled patients for each dosing regimen were not provided it was assumed that subjects were evenly allocated to each dosing regimen (one study).</td>
</tr>
<tr>
<td></td>
<td>1.5 When the number of patients changed over the study period, the average number of patients was used.</td>
</tr>
<tr>
<td></td>
<td>1.6 If in the same study other approaches were used to measure adherence apart from MEMS then only the number of patients associated with MEMS was used.</td>
</tr>
<tr>
<td>2. Dosing regimen</td>
<td>2.1 If the dosing regimen was not directly reported then it was implied from other content in that study where possible.</td>
</tr>
<tr>
<td></td>
<td>2.2 If the dosing regimen was specified as more than 1 schedule (e.g. once or twice daily) then the regimen was set to the average (e.g. 1.5 times daily).</td>
</tr>
<tr>
<td></td>
<td>2.3 If the dosing regimen was reported as twice daily plus then the regimen was set to 2.5 (one study).</td>
</tr>
<tr>
<td></td>
<td>2.4 If the number of patients per dosing regimen assigned to MEMS was not reported then the dosing regimen was set to the mode of the dosing regimen for all patients (one study).</td>
</tr>
<tr>
<td>3. Age</td>
<td>3.1 If the age of an individual group was not provided then the average age of all enrolled patients was used.</td>
</tr>
<tr>
<td></td>
<td>3.2 If both mean and median age were provided then mean age was used.</td>
</tr>
<tr>
<td></td>
<td>3.3 If mean age was not provided then median age was used.</td>
</tr>
<tr>
<td></td>
<td>3.4 If age was reported in terms of the percentage of patients with each age range then the mode of the age was selected.</td>
</tr>
</tbody>
</table>
### Result

### Assumptions

| 4. Adherence result | 4.1 If more than one value for adherence was reported (for instance adherence could be reported over different time periods) then the average adherence was used.  
|                     | 4.2 If both mean and median adherence results were provided then mean adherence result was used.  
|                     | 4.3 If mean adherence result was not provided then median adherence result was used.  
|                     | 4.4 If only one adherence result value was reported, the same adherence result value was used for each regimen (e.g. OD, BID) in that study. This assumption was used for 5 out of 36 studies. |
A.1.2. Diagnostic plots

**Figure A.1.1:** Observed adherence percentage vs Individual predicted adherence percentage. X-axis is Individual predicted adherence percentage and Y-axis is Observed adherence percentage.

**Figure A.1.2:** Weight residual vs Disease. X-axis is Disease where 0=hypertension and 1=HIV. Y-axis is Weighted residual.
Figure A.1.3: Weight residual vs Age (years). X-axis is Age (years). Y-axis is Weighted residual.

Figure A.1.4: Weight residual vs Dosing regimen. X-axis is Dosing regimen where 1=once daily, 2=twice daily, 3=thrice daily and 4=four times daily. Y-axis is Weighted residual.
A.1.3. Sensitivity analysis

Figure A.1.5: Weighted contribution of each study to the objective function value (equivalent to minus twice the log-likelihood). X-axis is Study ID and Y-axis is Weighted contribution to the objective function value.
A.1.4. Scatter matrix plots between each factor

Figure A.1.6: Scatter matrix plots between each factor. The top panel: Age (years) vs Disease, the middle panel: Age (years) vs Dosing regimen and the bottom panel: Dosing regimen vs Disease.
Appendix 2: Appendix to Chapter 4
A.2.1. Participant Information Sheet and Consent Form

Participant Information Sheet

Study title: Investigation of medication taking behaviour
Locality: Musselburgh Pharmacy, Dunedin, New Zealand
Ethics committee ref.: 12/STH/7
Lead investigator: Dr Rhiannon Braund
Contact phone number: (03) 479 7240

You are invited to take part in a study investigating medication taking behaviour. Whether or not you take part is your choice. If you don’t want to take part, you don’t have to give a reason, and it won’t affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you’d like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. We expect this will take about 5-10 minutes. You may also want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 4 pages long, including the Consent Form. Please make sure you have all the pages.

Why are we doing the study?

This study is part of a larger study investigating medication taking behaviour. Since many patients sometimes forget to take their medications, this study aims to find out how often this happens and whether or not the condition being treated makes a difference.

The study will use a medication event monitoring system (MEMS), which is a device with the ability to record the exact time and date that a medication bottle is opened, to record your medication taking patterns. This study aims to look at the feasibility of conducting a larger study. The specific objective is to identify any barriers which may occur in the larger study and assess how these may be overcome.

The study is funded by Lottery Health Research Fund. The principal investigator on this study is Dr Rhiannon Braund, School of Pharmacy, University of Otago with close support from Professor Stephen Duffull, School of Pharmacy, University of Otago. This study will be conducted by Piyanan Assawasuwannakit, School of Pharmacy, University of Otago as part...
of her PhD. If you have any questions or would like further information about the study, please feel free to contact Dr Rhiannon Braund at (03) 479 7240.

The study has been approved by the Southern Health and Disability Ethics Committees.

What would your participation involve?

You will receive one of your medications dispensed into a MEMS bottle instead of your regular tablet bottle. You should take your medication as you normally would. You will also be given a numbered courier bag and requested to return your MEMS bottle within 5 days after finishing your medication. If you do not return your MEMS bottle, you will be contacted by phone. Additionally, if your MEMS bottle is damaged or lost, this will be recorded to identify how this occurred and how this could be minimised in a future study.

You will also be requested to answer and return a questionnaire along with your MEMS bottle in the provided courier bag. The questionnaire will ask for your comments of the acceptability of the use of the MEMS bottle.

What are the possible benefits and risks to you of participating?

In the study, all your medications will remain exactly as prescribed. Since only one of your medications will be dispensed into a MEMS bottle instead of your regular tablet bottle, we do not expect any additional risks to you from participating. There are no direct benefits of this study participation as you will take all of your medications as you normally do.

What are the rights of participants in the study?

Your participation is voluntary. It is your choice to either choose to participate or choose not to participate in this study. If you choose not to participate, there will be no disadvantages to you of any kind. If you choose to participate, you are free to withdraw from the study at any time and there will be no disadvantages to you of any kind either.

You may advise us if you wish to be informed of the results of this study. However, this process will be delayed between the period of data collection and publication.

To ensure the privacy and confidentiality of individuals, data will be stored in a locked cabinet in the School of Pharmacy, University of Otago which only Piyanan Assawasuwannakiti and the other two investigators (Dr Rhiannon Braund and Professor Stephen Duffull) have access to the key.

What will happen after the study ends?

The data collected will be securely stored in such a way that only those mentioned above will be able to gain access to it. At the end of the project, any personal information will be destroyed except that any raw data on which the results of the project depend will be retained in secure storage for 10 years, after which they will be destroyed.
Results of this study may be published in a peer-review scientific journal without any data being linked to any individual participant. No material which could personally identify you will be used in any reports or shared with your pharmacist or doctor.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Dr Rhiannon Braund, School of Pharmacy, University of Otago
(03) 479 7240
rhiannon.braund@otago.ac.nz

If you want to talk to someone who isn’t involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 655 050
Fax: 0800 2 SUPPORT (0800 2767 7678)
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: (04) 816 2053
Email: hdecs@moh.govt.nz
Consent Form

Declaration by participant:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Participant's name: ____________________________

Signature: ____________________________ Date: ____________________________

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher’s name: ____________________________

Signature: ____________________________ Date: ____________________________
This appendix is partially based on the following peer-reviewed publication:

A.3.1. Parametric simulation of imperfect adherence patterns

A.3.1.1. Timing variability parametric distribution

A bimodal normal distribution was fitted to the imperfect timing data. A general form is given by

\[ F_{\text{timing}} = p(N(\mu_1, \sigma_1^2)) \times (1 - p)(N(\mu_2, \sigma_2^2)) \]

Equation A.3.1: Bimodal normal distribution for timing pattern errors

where \( F_{\text{timing}} \) denotes the form of the bimodal normal distribution for timing pattern errors, \( p \) is the probability of an actual dosing time being in the first normal distribution which is centred around the nominal dosing time, with mean \( \mu_1 \) and variance \( \sigma_1^2 \). \( 1 - p \) is the probability of an actual dosing time being in a second normal distribution which is delayed with respect to the nominal dosing time and has a mean of \( \mu_2 \) and variance of \( \sigma_2^2 \).

The parameters \( (p, \mu_1, \sigma_1^2, \mu_2, \sigma_2^2) \) were estimated from the data arising from the index adherence profile (shown in Figure 5.1). Missing dose data were excluded when these parameters were estimated.

The mode of the timing of doses taken was 5:24 am. Therefore, the difference of timing from the mode at 5:24 am was 0 which was used as an index time. The bimodal distribution parameter estimates are presented in Table A.3.1.

Table A.3.1: Bimodal normal distribution parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p )</td>
<td>0.91</td>
</tr>
<tr>
<td>( \mu_1 )</td>
<td>1.07 hours after the index time 0</td>
</tr>
<tr>
<td>( \sigma_1^2 )</td>
<td>0.92 hours</td>
</tr>
<tr>
<td>( \mu_2 )</td>
<td>7.48 hours after the index time 0</td>
</tr>
<tr>
<td>( \sigma_2^2 )</td>
<td>4.69 hours</td>
</tr>
</tbody>
</table>
A.3.1.2. Random missed doses parametric distribution

Random missed doses were assumed to follow a Poisson process. Where two consecutive missed doses occurred, they were considered as two cases of an individual random missed dose. The mean number of random missed doses was calculated. The resulting Poisson distribution is given by

\[ F_{\text{missed doses}} = \frac{\lambda^x}{x!} e^{-\lambda}; x = 0, 1, 2, ..., \infty \]

**Equation A.3.2: Likelihood of a missed dose**

where \( F_{\text{missed doses}} \) is the likelihood of a missed dose given the expected rate of missed doses to be \( \lambda \) for a 150 dose period. When simulating the occurrence of missed doses, the total number of missed doses (\( N_{\text{missed doses}} \)) were generated from the Poisson distribution and these were randomly assigned to the dosing period by drawing \( N_{\text{missed doses}} \) random discrete uniform numbers from the interval (1, 150) and assigning the dose on these occurrences as missing (=0 mg). These assignments were assessed for whether there were more than 2 consecutive missed doses in which case the profile was discarded and replaced with a new simulation. This is to avoid additional drug holidays occurring.

According to the index adherence profile, the estimated mean number of random missed doses over 150 days was 13.
A.3.1.3. Drug holidays parametric distribution

An empirical frequency distribution was used for drug holidays. Here, a drug holiday was considered as three consecutive missed doses. The number of drug holidays over 150 days was given by

\[ F_{\text{holidays}} = \frac{f_i}{N} \times 100; i = 0,1,2,3 \]

**Equation A.3.3: Likelihood of drug holidays**

where \( F_{\text{holidays}} \) is the likelihood of drug holidays happening over 150 days, a maximum of 3 drug holidays was considered permissible, \( f_i \) is the density for the \( i \)th drug holiday and \( \sum_{i=1}^{3} f_i = 1 \), \( N \) is the maximum number of drug holidays in the population. Samples drawn from this distribution to determine the number of drug holidays per 150 day profile. The timing of the drug holiday was based on drawing a uniform discrete random number in the range of (1, 150). A profile was discarded if a drug holiday was consecutive with a missing dose, in which case the profile was replaced with a new simulation. Consecutive drug holidays were, however, allowed.

The likelihood of drug holidays happening as 0, 1, 2 and 3 times over 150 days were 0.43, 0.3, 0.17, and 0.09, respectively.

Example simulation profiles were generated to assess for patterns (see Figure A.3.1 for 4 typical examples).
Figure A.3.1: Example simulated profiles of imperfect adherence. The X-axis is day. The Y-axis is the difference of timing from the first mode in hours. Each blue dot represents the time difference. Green vertical bars depict random missed doses. Red vertical bars depict drug holidays.
A.3.2. Warfarin population kinetic-pharmacodynamic model

The schematic and details of the Hamberg model is shown in Figure A.3.2 (Adapted from Hamberg et al. [229] and Wright & Duffull [230]).

\[
\frac{dA}{dt} = -k_e \times A
\]

\[
\frac{dC_{11}}{dt} = (1 - E) \times \frac{3}{MTT_{C1}} - C_{11} \times \frac{3}{MTT_{C1}}
\]

\[
\vdots
\]

\[
\frac{dC_{13}}{dt} = C_{12} \times \frac{3}{MTT_{C1}} - C_{13} \times \frac{3}{MTT_{C1}}
\]

\[
\frac{dC_{21}}{dt} = (1 - E) \times \frac{3}{MTT_{C2}} - C_{21} \times \frac{3}{MTT_{C2}}
\]

\[
\vdots
\]

\[
\frac{dC_{23}}{dt} = C_{22} \times \frac{3}{MTT_{C2}} - C_{23} \times \frac{3}{MTT_{C2}}
\]

\[
k_e = \frac{CL_s}{V_s}
\]

\[
DR = A \times k_e
\]

\[
EDK_{50} = CL_s \times EC_{50}
\]

\[
E = \frac{E_{max} \times DR^y}{EDK_{50}^y + DR^y}
\]
Figure A.3.2: Schematic and details of the Hamberg model. There are two transit chains, C1 and C2 with three compartments each which account for warfarin delayed effects. Initial condition for an input compartment was 0 and transit compartments was 1.

A amount of drug in the body. $C_{11}, C_{12}, C_{13}$ compartment 1, 2, 3 respectively in the transit chain $C_1$. $C_{21}, C_{22}, C_{23}$ compartment 1, 2, 3 respectively in the transit chain $C_2$.

$MTT$ mean transit time. $k_e$ first order elimination rate constant. $CL_s$ $s$-warfarin clearance. $V_s$ volume of distribution. $DR$ dose driving rate. $EDK_{50}$ dose rate for 50% inhibition of coagulation. $EC_{50}$ $s$-warfarin concentration resulting in half maximal effect. $E$ inhibitory effect on vitamin K epoxide reductase. $E_{max}$ maximum inhibition of coagulation. $\gamma$ Hill coefficient.

INR was derived from:

$$E[INR] = INR_{BASE} + INR_{max} \times \left( 1 - \frac{C_{13} + C_{23}}{2} \right)$$

Equation A.3.4: Expected INR

where $E[INR]$ is expected INR. $INR_{BASE}$ is INR at baseline. $INR_{max}$ is the maximum INR which was used as 20 according to the Hamberg model.

Model parameters are shown in Table A.3.2.

Additive residual variability was added to log transformed data in the Hamberg model. Therefore, in this study, proportional residual variability was incorporated to the response.
Table A.3.2: Warfarin model parameters

<table>
<thead>
<tr>
<th>Warfarin model parameter</th>
<th>Population estimate</th>
<th>BSV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL_s$ (L/h)</td>
<td>0.348</td>
<td>29.8</td>
</tr>
<tr>
<td>$V_s$ (L)</td>
<td>14.3</td>
<td>23.2</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>$EC_{50}$ (mg/L)</td>
<td>4.1</td>
<td>33.2</td>
</tr>
<tr>
<td>Gamma</td>
<td>1.15</td>
<td>-</td>
</tr>
<tr>
<td>MTT1 (h)</td>
<td>28.6</td>
<td>-</td>
</tr>
<tr>
<td>MTT2 (h)</td>
<td>118.3</td>
<td>-</td>
</tr>
<tr>
<td>INR$_{\text{base}}$</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>INR$_{\text{max}}$</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Proportional RUV</td>
<td>20</td>
<td>-</td>
</tr>
</tbody>
</table>

$CL_s$ = warfarin clearance, $V_s$ = volume of distribution, $E_{\text{max}}$ = maximum inhibition of coagulation, $EC_{50}$ = warfarin concentration resulting in half maximal effect, Gamma = Hill coefficient, MTT1 = mean transit time chain 1, MTT2 = mean transit time chain 2, INR$_{\text{base}}$ = INR at baseline, INR$_{\text{max}}$ = maximum INR, RUV = residual unexplained variability.

A.3.3. Further exploration on dabigatran

A.3.3.1. Methods

The model used for dabigatran in this study was a population PKPD model for healthy volunteers and patients with atrial fibrillation or undergoing orthopaedic surgery developed by Dansirikul et al. [277] The model was described by a two compartment disposition model. The model and parameter values are taken from [277] and are provided in Table A.3.3. The dose was set to 300 mg once daily for 150 days. Successful attainment of a treatment target was considered as time in the therapeutic range. The once daily dose was calibrated so that the typical patient achieved the midpoint of the therapeutic range. Time to steady state was assumed at 20 days, to parallel the warfarin example. Note there is no defined therapeutic range for dabigatran and also no typical time in the therapeutic range. Dabigatran is a direct inhibitor of factor IIa, which has
similarities to one of the purported actions of unfractionated heparin. Its activity is often measured using Activated Partial Thromboplastin Time (aPTT) and values ranging from 50 to 75 seconds were chosen as therapeutic which are similar to therapeutic aPTT values for heparin. The time in the therapeutic range was set to 70%. These values were chosen for illustrative purposes only and are not intended to be considered as a therapeutic range.

Table A.3.3: Dabigatran model parameters

<table>
<thead>
<tr>
<th>Dabigatran model parameter</th>
<th>Population estimate</th>
<th>BSV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>111</td>
<td>-</td>
</tr>
<tr>
<td>V1/F (L)</td>
<td>728</td>
<td>26.1</td>
</tr>
<tr>
<td>Q/F (L/h)</td>
<td>35.5</td>
<td>-</td>
</tr>
<tr>
<td>V2/F (L)</td>
<td>345</td>
<td>-</td>
</tr>
<tr>
<td>Ka (/h)</td>
<td>0.754</td>
<td>95.3</td>
</tr>
<tr>
<td>ALAG(h)</td>
<td>0.634</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>1.00</td>
<td>44.7</td>
</tr>
<tr>
<td>Emax (sec)</td>
<td>16.6</td>
<td>27.7</td>
</tr>
<tr>
<td>EC50 (ng/mL)</td>
<td>184</td>
<td>53.0</td>
</tr>
<tr>
<td>Baseline (sec)</td>
<td>33</td>
<td>8.49</td>
</tr>
<tr>
<td>Slope (sec/ng/mL)</td>
<td>0.0574</td>
<td>33.5</td>
</tr>
<tr>
<td>Proportional RUV</td>
<td>-</td>
<td>8.39</td>
</tr>
</tbody>
</table>

CL/F = apparent total body clearance. V1/F = apparent central volume of distribution. Q/F = apparent intercompartmental clearance. V2/F = apparent peripheral volume of distribution. Ka = first-order absorption rate constant. ALAG = absorption lag time. F = oral bioavailability. Emax = maximum effect, EC50 = concentration resulting in half maximal effect, Baseline = aPTT baseline, Slope = Slope in a combination of a linear and an Emax model for aPTT. RUV = residual unexplained variability.

The concentration in the central compartment drives the effect.

\[ E = \frac{E_{\text{max}} \times C}{EC_{50} + C} \]

Equation A.3.5: Effect of dabigatran

where \( E \) is effect. \( C \) is drug concentration.
Subsequently, aPTT was derived from a combination of a linear and an $E_{\text{max}}$ model.

$$a\text{PTT} = \text{base} + E + \text{slope} \times C$$

**Equation A.3.6: aPTT derived from a combination of a linear and an $E_{\text{max}}$ model**

where $\text{base}$ is aPTT at baseline. $\text{slope}$ is the slope of the linear relationship. Proportional residual variability was incorporated to the response.

### A.3.3.2. Results

The probability of therapeutic success, $P_{\text{ip}}$, for dabigatran was 0.58 and $P_p$ was 0.69 which resulted in a RF of 0.62. This means that for dabigatran therapeutic success was almost 38% less likely with imperfect adherence. Different choices of time in therapeutic range and the range itself will change these values.

### A.3.3.3. Discussion

Dabigatran, a direct reversible thrombin inhibitor, has a shorter half-life of 12-17 hours and is a competitive antagonist of factor IIa. Therefore, it has none of the intermediate effects seen with warfarin. Due to these two characteristics, it is likely that dabigatran would be less forgiving than warfarin. Given that there was no established marker of coagulation, or a range for this marker or a percent time in this range then a direct comparison of the forgiveness of dabigatran is not formally possible. In this work, the marker aPTT, with a therapeutic range of 50 to 75 seconds and a time in this range to determine success of at least 70% was used. It is seen under these assumptions that dabigatran has a RF value of 0.62. It is noted that while dabigatran is generally prescribed twice daily in clinical practice, in this study, dabigatran was given once daily to parallel once daily profiles of imperfect adherence used in the warfarin example. Although it could not be concluded that dabigatran is less forgiving than warfarin, the dabigatran PD characteristics suggested that caution should still be applied when prescribing this drug to patients with known poor adherence.
A.3.4. MATLAB® code for the illustrative example

Run file (run_illus)

% A 1-compartment instantaneous unit input PK model linked to an immediate effects E_{max} PD model was used.

clear all
clc

rep=1000; % set 1000 replicates
ss_start=11; % set when steady state starts
crit=0.35; % set a criterion one value: Effect at trough is greater than crit.
crit2=0.9; % set a criterion two value: Fraction of doses where crit one must be true.

d=1; % dose (mg)
t=[0:0.1:150]; % time (days) note half-life=1 day, treatment period=150 days

dn_total=150; % total number of prescribed doses
dn_taken=150; % number of doses taken. This is the case for perfect adherence where dn_total=dn_taken.
perfect_profile=[0:1:150]; % perfect adherence profile

use_perfect=1; % change to either 0 or 1 for imperfect adherence and perfect adherence, respectively

%% call a init_PKPD_param file.
init_PKPD_param

%% run
for j=1:rep;
    if use_perfect==0; % for imperfect adherence
        init_profilegenerator; % call an init_profilegenerator file.
        profile_generator; % call a profile_generator file.
    else
        dosetime=perfect_profile; % time to give each dose for perfect adherence
    end

    for dn=1:dn_taken; % dose number
        k=cl(j)/v(j);
        aa=(t<dosetime(dn));
        C(dn,:)=d/v(j)*exp(-k*(t-dosetime(dn))).*(1-aa);
    end

    Ct(j,:)=sum(C);
    E(j,:)=(Emax(j)*Ct(j,:))/(EC50(j)+Ct(j,:));
    eps=normrnd(0,0.1,size(t));
    E(j,:)=E(j,:)*exp(eps); % proportional residual unexplained variability
criteria; % call a crieteria file. See code below.
plot_the_profile; % call a plot_the_profile file.
Appendix 3: Appendix to Chapter 5

```matlab
subplot(3,1,2);
plot(t,E); % effect-time profile
xlabel('dose interval')
ylabel('effect')
set(gca,'xtick',0:10:150)

subplot(3,1,3);
plot(t,Ct) % concentration-time profile
xlabel('dose interval')
ylabel('concentration')
set(gca,'xtick',0:10:150)
end

success=sum(success_j); % compute success

init_PKPD_param

%% Initialising PKPD parameters

%% parameters
mean_v=1; %L
mean_cl=log(2); %L/h
mean_Emax=1;
mean_EC50=1.3; %mg/L

%% BSV
BSV_parPK=[0.09 0; 0 0.09]; % BSV=30% on v and cl
BSV_parPD=[0.09 0; 0 0.09]; % BSV=30% on Emax and EC50

%% simulation parameters

% simulating PK parameters
par=exp(mvnrnd([log(mean_v) log(mean_cl)], BSV_parPK, rep));
v=par(:,1);
cl=par(:,2);

% simulating PD parameters
par=exp(mvnrnd([log(mean_Emax) log(mean_EC50)], BSV_parPD, rep));
Emax=par(:,1);
EC50=par(:,2);

Genertating parameters of timing to obtain paramEsts for init_profilegenerator

%% Generating parameters of diff_tm_i (diff_tm_i is the difference of timing from the mode of drug taking)

% Data were extracted from the index adherence profile.
clear all

% timing distribution
diff tm=[-1.85,-0.7,-0.23,-0.1,-0.08,-0.05,0.01,0.01,0,0,0,0,0,0,0.01,...
0.03,0.04,0.08,0.1,0.1,0.12,0.14,0.16,0.17,0.17,0.23,0.23,0.23,...
0.24,0.25,0.27,0.28,0.29,0.3,0.31,0.33,0.33,0.34,0.35,0.35,...
0.35,0.76,0.77,0.77,0.79,0.8,0.81,0.83,0.83,0.83,0.84,0.85,...
0.85,0.87,0.87,0.88,0.89,0.89,0.91,0.91,0.92,0.93,0.93,0.94,0.96,...
0.97,0.98,1.01,1.03,1.04,1.05,1.06,1.07,1.08,1.13,1.13,1.14,...
1.15,1.15,1.16,1.19,1.21,1.23,1.27,1.31,1.33,1.33,1.34,1.77,1.78,...
1.79,1.81,1.82,1.85,1.9,1.92,1.92,1.96,1.96,2.05,2.07,2.11,2.13,...
2.14,2.16,2.17,2.18,2.23,2.24,2.26,2.26,2.33,2.34,2.35,2.8,...
2.86,2.87,2.9,2.95,3,3.01,3.29,3.85,4.17,4.25,6.34,7.77,8.77,8.92,...
11.35,14.09,16.1];

pdf_normmixture = @(diff_tm,p,mu1,mu2,sigma1,sigma2)
    p*normpdf(diff_tm,mu1,sigma1) + (1-p)*normpdf(diff_tm,mu2,sigma2);

pStart = .8;
muStart = [1.13,10.48];
sigmaStart = [1.02,3.54];
start = [pStart muStart sigmaStart];

lb = [0 -Inf -Inf 0 0];
ub = [1 Inf Inf Inf Inf];

paramEsts = mle(diff_tm, 'pdf',pdf_normmixture, 'start',start,
    'lower',lb, 'upper',ub);

statset('mlecustom');

options = statset('MaxIter',300, 'MaxFunEvals',600);
paramEsts = mle(diff_tm, 'pdf',pdf_normmixture, 'start',start,...
    'lower',lb, 'upper',ub, 'options',options);

init_profilegenerator

%% Setting up profile generator

%% Drug holidays

% drug holiday (dh) distribution
dh=[0,0,0,0,0,0,0,0,0,0,0,0,1,1,1,1,1,1,2,2,2,2,3,3];

% generating dh random deviates
r=randi([1 length(dh)]);
dh_i=dh(r);

%% Random missed doses

% random missed doses (md) distribution
possible_md = 0:1:150;
mean_md = 13;

% generating md random deviates
md_i=poissrnd(mean_md);

%% Timing for bimodal normal probability, mu1, mu2, sigma1, sigma2
paramEsts= [ 0.9145 1.0725 7.4758 0.9176 4.6886 ];
p=paramEsts(1,1);
mu1Est=paramEsts(1,2);
mu2Est=paramEsts(1,3);
sigma1Est=paramEsts(1,4);
sigma2Est=paramEsts(1,5);

profile_generator

%% Generating an adherence profile for imperfect adherence

count=0;
fflag=10;
while fflag ==10 & count < 100
    fflag=0;
    count=count+1;

    % Start day(s) of drug holidays (ini_day_dh)
    if dh_i==1; % 1 drug holiday
        ini_day_dh=randsample(dn_total-2,1);
    end

    if dh_i==2; % 2 drug holidays
        ini_day_dh=randsample(dn_total-2,2);
    end

    if dh_i==3; % 3 drug holidays
        ini_day_dh=randsample(dn_total-2,3);
    end

    % position(s) of drug holidays (position_dh_i)
    if dh_i==1;
        position_dh_i=ini_day_dh:2+ini_day_dh;
    end

    if dh_i==2;
        position_dh_i=[ini_day_dh(1,1):2+ini_day_dh(1,1),ini_day_dh(2,1):2+ini_day_dh(2,1)];
    end

    if dh_i==3;
        position_dh_i=[ini_day_dh(1,1):2+ini_day_dh(1,1),ini_day_dh(2,1):2+ini_day_dh(2,1),ini_day_dh(3,1):2+ini_day_dh(3,1)];
    end

    % possible positions of missed doses
a=[1:1:150];

if dh_i==0;
    a=[1:1:150];
    b=setdiff(a,position_dh_i);
end

%% positions of missed doses (position_md_i)
if dh_i==0;
    position_md_i=randsample(b,md_i);
else
    position_md_i=randsample(a,md_i);
end

%% then generating timing deviates
if dh_i==0;
    dn_taken=dn_total-(md_i);
end

if dh_i==1;
    dn_taken=dn_total-(md_i)-(dh_i*3));
end

if dh_i==2;
    u=union(position_dh_i(1,1:3),position_dh_i(1,4:6));
    dn_taken=dn_total-(md_i)-(length(u));
end

if dh_i==3;
    u2=union(position_dh_i(1,1:3),position_dh_i(1,4:6));
    uu=union(u2,position_dh_i(1,7:9));
    dn_taken=dn_total-(md_i)-(length(uu));
end

clear diff_tm_i
for q=1:dn_taken;
    if rand()<p;
        diff_tm_i(q) = normrnd(mu1Est,sigma1Est);
    else
        diff_tm_i(q) = normrnd(mu2Est,sigma2Est);
    end
end

%% criteria to discard unacceptable profiles
% discard random missed doses occurring at least 3 doses consecutively
if length(strfind(diff(sort(position_md_i)),[1 1]))>0
    fflag=10;
end

% when dh_1==1, discard a random missed dose occurring right before dh at least one point of time in the profile
if dh_i==1;
    position_md_i_plus_1=position_md_i+1;
    combined_1_plus=horzcat(position_md_i_plus_1,position_dh_i);
    if length(strfind(diff(sort(combined_1_plus)),[0]))>0;
        fflag=10;
    end

% when dh_1==1, discard a random missed dose occurring right after dh at least one point of time in the profile
if dh_i==1;
    position_md_i_minus_1=position_md_i-1;
    combined_1_minus=horzcat(position_md_i_minus_1,position_dh_i);
    if length(strfind(diff(sort(combined_1_minus)),[0]))>0;
        fflag=10;
    end
end

% when dh_1==2, discard a random missed dose occurring right before dh at least one point of time in the profile
if dh_i==2;
    position_md_i_plus_1=position_md_i+1;
    u=union(position_dh_i(1,1:3),position_dh_i(1,4:6));
    combined_2_plus=horzcat(position_md_i_plus_1,u);
    if length(strfind(diff(sort(combined_2_plus)),[0]))>0;
        fflag=10;
    end
end

% when dh_1==2, discard a random missed dose occurring right after dh at least one point of time in the profile
if dh_i==2;
    position_md_i_minus_1=position_md_i-1;
    u2=union(position_dh_i(1,1:3),position_dh_i(1,4:6));
    uu=union(u2,position_dh_i(1,7:9));
    combined_2_minus=horzcat(position_md_i_minus_1,uu);
    if length(strfind(diff(sort(combined_2_minus)),[0]))>0;
        fflag=10;
    end
end

% when dh_1==3, discard a random missed dose occurring right before dh at least one point of time in the profile
if dh_i==3;
    position_md_i_plus_1=position_md_i+1;
    u2=union(position_dh_i(1,1:3),position_dh_i(1,4:6));
    uu2=union(u2,position_dh_i(1,7:9));
    combined_3_plus=horzcat(position_md_i_plus_1,uu2);
    if length(strfind(diff(sort(combined_3_plus)),[0]))>0;
        fflag=10;
    end
end

% when dh_1==3, discard a random missed dose occurring right after dh at least one point of time in the profile
if dh_i==3;
    position_md_i_minus_1=position_md_i-1;
    u2=union(position_dh_i(1,1:3),position_dh_i(1,4:6));
    uu2=union(u2,position_dh_i(1,7:9));
    combined_3_minus=horzcat(position_md_i_minus_1,uu2);
    if length(strfind(diff(sort(combined_3_minus)),[0]))>0;
        fflag=10;
    end
end

%% positions of timing
clear position_diff_tm_i

if dh_i==0;
    position_diff_tm_i=setdiff(a,position_md_i);
end

if dh_i==1;
    position_diff_tm_i=setdiff(a,union(position_md_i,position_dh_i));
end

if dh_i==2;
    position_diff_tm_i=setdiff(a,union(position_md_i,position_dh_i));
end

if dh_i==3;
    position_diff_tm_i=setdiff(a,union(position_md_i,position_dh_i));
end
end

%% computing dose time
if count > 99
    stop1
end
if fflag==10
    stop2
end

dt1=[position_diff_tm_i]*24;
dt2=dt1+[diff_tm_i];
dt3=dt2/24;  %Index a dose interval back to 1

dosetime=[0,dt3];

criteria

criteria for success

for i=ss_start:length(dosetime);  %ignore first nonsteady state times
dose time is a vector of dose times
    aaa=dosetime(i);
    bb=max(find(t<aaa));  %t is a vector of sampling times
    trough(i+1-ss_start)=t(bb);
    eff=E(j,bb);
    success_ij(i+1-ss_start)=eff>crit;
end

suma=sum(success_ij);
success_j(j)=suma/length(success_ij) > crit2;
%% plot the profile of imperfect adherence

x=position_md_i;
y=repmat(24,1,length(x));

if dh_i==1;
xx=position_dh_i;
yy=repmat(24,1,length(xx));
end

if dh_i==2;
xx=u;
yy=repmat(24,1,length(xx));
end

if dh_i==3;
xx=uu;
yy=repmat(24,1,length(xx));
end

figure;

subplot(3,1,1);
hold on
scatter(position_diff_tm_i,diff_tm_i);
bar(x,y,0.3,'g')
if dh_i~=0;
bar(xx,yy,0.3,'r')
end
hold off

xlabel('day')
ylabel('difference of timing')
set(gca,'xtick',0:10:150)
set(gca,'ytick',-4:4:20)
ylim([-4 20])
A.3.5. MATLAB® code for the warfarin example

Run file (run_warfarin)

%%% Based on Hamberg et al. A pharmacometric model describing the relationship between warfarin dose and INR response with respect to variations in CYP2C9, VKORC1, and age. Clin Pharmacol Ther 2010; 87: 727-34.

clear all
clc

rep=1000;

%%% independent variables
d=3.5; % dose = 3.5 mg

dn_total=150;

crit=2; % INR=2
crit2=3.5; % INR=3.5

TTR_success=0.55; % Successful treatment=at least 55% of steady state trough values were within the therapeutic INR range success

perf_adh=1; % perf_adh=1 is perfect adherence
% perf_adh=0 is imperfect adherence

options = odeset('RelTol',1e-6);

for ii=1:rep;
    inits = [d 1 1 1 1 1 1]; % initial condition for each compartment
    start=1;
    time_dose=0;
    init_PKPD_warfarin_param % call an init_PKPD_warfarin_param file.
    KDE=cl_s(ii)/v_s(ii);
    EDK50=cl_s(ii)*EC50(ii);
    if perf_adh==1 % for perfect adherence
        init_profilegenerator_perfect % call an init_profilegenerator_perfect file.
    profile_generator_perfect % call a profile_generator_perfect file.
    else
        init_profilegenerator % for imperfect adherence. Call the init_profilegenerator file. (See code in the illustrative example)
    end
    profile_generator % for imperfect adherence. Call the profile_generator file. (See code in the illustrative example)
end
for jj=1:dn_taken
    D=[d 0 0 0 0 0]; % initial condition of dose for each compartment
    if jj==1;
        di=(dt2(1,1));
    else
        di=(dt2(1,jj)-dt2(1,jj-1));
    end
    if dt2(1,jj)<dt2(1,jj-1);
        di=1;
    end
end

% In this code T is the time for the whole profile from time=0 and TT is the time within a dose interval.

    TT=[0:1:di]; % di=dose interval
    stop=start+length(TT)-1; % stop position of vector T and F for dose jj
    sol=ode45(@ode_warfarin,[0 di],[inits,options,KDE,Emax,gamma,EDK50,mtt1,mtt2]); % pass arguments to ODE function

    A4=deval(sol,TT,4); % amount in compartment 4
    A7=deval(sol,TT,7); % amount in compartment 7
    INR=INRbase+INRmax*(1-(A4+A7)/2); % compute INR
    eps=normrnd(0,0.2,size(TT));
    INR=INR.*exp(eps);
    inits=deval(sol,di)'+D;
    F(ii,start:stop)=INR; % response
    T(ii,start:stop)=TT+time_dose; % time for the whole profile
    start=start+1;
    time_dose=time_dose+di; % time of the dose
    Trough_INR(jj)=INR(length(TT));
    Trough_INR_ss=Trough_INR(21:length(Trough_INR));
end

criterion_warfar % call a criterion_warfar file
end

overall_success = sum(success_outcome); % compute overall success
overall_success
fractional_overall_success = overall_success / rep; % compute fractional overall success

init_PKPD_warfarin_param

%% Initialising warfarin PKPD parameters

%% parameter values
cl_s=0.348; % L/h
v_s=14.3; % L
Emax=1;
gamma=1.15;
EC50=4.1; % mg/L
mtt1=28.6; % h
mtt2=118.3; % h
INRbase=1;
INRmax=20;

%% BSV
BSV_parPK=[0.0894 0; 0 0.0538];
BSV_parPD=[0.1156];

%% simulation parameters
% simulating PK parameters
par=exp(mvnrnd([log(cl_s) log(v_s)], BSV_parPK, rep));
cl_s=par(:,1);
v_s=par(:,2);

% simulating PD parameters
par=exp(mvnrnd([log(EC50)], BSV_parPD, rep));
EC50=par(:,1);

init_profilegenerator_perfect

%% Setting up profile generator for perfect adherence

%% Drug holidays
% dh distribution
dh=[0,0,0,0,0,0,0,0,0,0,0,0];

% generating dh random deviates
r=randi([1 length(dh)]);
dh_i=dh(r);

%% Random missed doses
md=[0,0,0,0,0,0,0,0,0,0,0,0];
r1=randi([1 length(md)]);
md_i=md(r1);

profile_generator_perfect

%% Generating an adherence profile for imperfect adherence
for q=1:dn_taken
    diff_tm_i(q) = 0;
end

ODE_warfarin

function dAdt=ode_warfarin(t,A,KDE,Emax,gamma,EDK50,mtt1,mtt2)
DR = KDE * A(1);

\[
\text{EFF} = \text{Emax} \times \text{DR}^{\gamma} / (\text{EDK50}^{\gamma} + \text{DR}^{\gamma});
\]

\[
dA/dt = \left[-\text{KDE} \times A(1) \right. \\
(1 - \text{EFF}) \times 3/\text{mtt1} - A(2) \times 3/\text{mtt1} \\
A(2) \times 3/\text{mtt1} - A(3) \times 3/\text{mtt1} \\
A(3) \times 3/\text{mtt1} - A(4) \times 3/\text{mtt1} \\
(1 - \text{EFF}) \times 3/\text{mtt2} - A(5) \times 3/\text{mtt2} \\
A(5) \times 3/\text{mtt2} - A(6) \times 3/\text{mtt2} \\
A(6) \times 3/\text{mtt2} - A(7) \times 3/\text{mtt2};
\]

\textit{criterion\_warf}

% criterion for success for warfarin

Trough\_INR\_ss = Trough\_INR((21:length(Trough\_INR)));

n\_trough = length(Trough\_INR\_ss);

success\_ind = (Trough\_INR\_ss > crit \& Trough\_INR\_ss < crit2); % individual success of different doses

success = sum(success\_ind); % success over all steady state doses

% success outcome tells us whether a single profile has been a success or not

fractional\_success = success/n\_trough;

if fractional\_success >= TTR\_success
    success\_outcome(ii)=1;
else
    success\_outcome(ii)=0;
end
Appendix 4: Appendix to Chapter 6
A.4.1. MATLAB® code for the atorvastatin example

Run file (run_atorvastatin)


clear all
clc

rep=1000;

%% independent variables

% pt 17
d=40*10^3; % mcg. Turn 1 patient on at a time with the corresponding dn_total and dn_taken

% pt 19
%d=80*10^3; % mcg

% pt 23
d=10*10^3; % mcg

% pt 17
% dn_total=103;
% dn_taken=90;

% pt 19
% dn_total=95;
% dn_taken=91;

% pt 23
% dn_total=91;
% dn_taken=90;

crit=2.6;

TTR_success=0.6;

use_perfect=1;

pt=17; % change this according to the patient

options = odeset('RelTol',1e-6);

for ii=1:rep;
    D=[d 0 0 0 0];
    start=1;
time_dose=0;

init_PKPD_param_atorvastatin % call an
init_PKPD_param_atorvastatin file

ka_ii=ka(ii);
clpm_ii=clpm(ii);
v1_ii=v1(ii);
clmp_ii=clmp(ii);
vm_ii=vm(ii);
Q_ii=Q(ii);
v2_ii=v2(ii);
clm_ii=clm(ii);

baseline_ii=baseline(ii); % baseline LDL
Emax_ii=Emax(ii);
EC50_ii=EC50(ii);
Rin_ini_ii=Rin_ini(ii);
kout_ii=Rin_ini_ii/baseline_ii;

inits = [0 0 0 0 baseline_ii];

if use_perfect==1;
    dn_taken=dn_total;
end

for jj=1:dn_taken
    if use_perfect==0;
        if pt==17;
            load('di_pt17.mat'); % actual dose interval of pt 17
            di=di_pt17{1,jj};
        end

        if pt==19;
            load('di_pt19.mat'); % actual dose interval of pt 19
            di=di_pt19{1,jj};
        end

        if pt==23;
            load('di_pt23.mat'); % actual dose interval of pt 23
            di=di_pt23{1,jj};
        end
    else
        dii=repmat(24,1,dn_taken);
        di=dii(1,jj); % dose interval for perfect adherence
    end

    TT=[0:1:di];
    stop=start+length(TT)-1;

    sol=ode45(@ode_atorvastatin,[0
              di],[inits,options,v1_ii,Emax_ii,EC50_ii,Rin_ini_ii,ka_ii,clpm_ii,clmp_ii,vm_ii,Q_ii,v2_ii,clm_ii,kout_ii]);

    A5=deval(sol,TT,5); % LDL amount
    LDL=A5/38.67; % convert LDL from mg/dL to mmol/L
Appendix 4: Appendix to Chapter 6

\[ \text{inits = deval(sol, di)' + D; } \\
\text{F(ii, start: stop) = LDL; } \\
\text{T(ii, start: stop) = TT + time_dose; } \\
\text{start = stop + 1; } \\
\text{time_dose = time_dose + di; } \\
\text{Trough_{LDL}(jj) = LDL(length(TT));} \\
\]

\begin{verbatim}
criterion_atorvastatin

plot(T(ii, :) / 24, F(ii, :))
xlabel('Time (days)')
ylabel('LDL (mmoL/L)')
xlim([0 110])
ylim([1 5])
set(gca, 'xtick', 0:10:110)
target = 2.6;
hline = refline([0 target]);
hline.Color = 'r';
\end{verbatim}

\end{verbatim}

\begin{verbatim}
overall_success = sum(success_outcome);
overall_success
fractional_overall_success = overall_success / rep
\end{verbatim}

\begin{verbatim}
\textit{init\_PKPD\_param\_atorvastatin}

%% Initialising PKPD parameters

%% parameter values
ka=3.5; % /h
clpm=504; % L/h
v1=3250; % L
clmp=24; % L/h
vm=137; % L
Q=1880; % L/h
v2=2170; % L
clm=116; % L/h
baseline=185; % mg/dL
Emax=0.489;
EC50=0.0868; % ng/mL
Rin_ini=1.14; % mg/dL/h

%% BSV
BSV_parPK=[0 0 0 0 0 0 0; 0 0.1183 0 0 0 0 0; 0 0 0.4502 0 0 0 0; 0 0 0 0.4914 0 0 0; 0 0 0 0 0 0 0; 0 0 0 0 0 0.2034]; % BSV on clpm, v1, vm, v2, clm

BSV_parPD=[0.0408 0 0 0; 0 0.0246 0 0; 0 0 0.8686 0; 0 0 0.252]; % BSV on baseline, Emax, EC50, Rin_ini

%% simulation parameters

% simulating PK parameters
parPK=exp([log(ka) log(clpm) log(v1) log(clmp) log(vm) log(Q) log(v2) log(clm)]);
ka=parPK(:,1);
clpm=parPK(:,2);
v1=parPK(:,3);
clmp=parPK(:,4);
vm=parPK(:,5);
Q=parPK(:,6);
v2=parPK(:,7);
clm=parPK(:,8);

% simulating PD parameters
parPD=exp([log(baseline) log(Emax) log(EC50) log(Rin_ini)]);

baseline=parPD(:,1);
Emax=parPD(:,2);
EC50=parPD(:,3);
Rin_ini=parPD(:,4);

function
dAdt=ode_atorvastatin(t,A,v1,Emax,EC50,Rin_ini,ka,clpm,clmp,vm,Q,v2,clm,kout)
C=(A(2)/v1);
E=1-((Emax*C)/(EC50+C));
Rin=Rin_ini;

dAdt=[-
ka*A(1)
ka*A(1)-clpm*A(2)/v1+clmp*A(4)/vm-Q*A(2)/v1+Q*A(3)/v2
Q*A(2)/v1-Q*A(3)/v2
clpm*A(2)/v1-clmp*A(4)/vm-clm*A(4)/vm
Rin*E-kout*A(5)];

function
criterion_atorvastatin
Trough_LDL_ss = Trough_LDL((20:length(Trough_LDL)));
n_trough = length(Trough_LDL_ss);
success_ind = (Trough_LDL_ss < crit);
success = sum(success_ind);
fractional_success = success/n_trough;

if fractional_success >= TTR_success
    success_outcome(ii)=1;
else
    success_outcome(ii)=0;
end
A.4.2. MATLAB® code for the omeprazole example

Run file (run_omeprazole)

```matlab

clear all
clc

rep=1000;

%% independent variables

% pt 3
d=20; % mg. Turn 1 patient on at a time with the corresponding dn_total and dn_taken

% pt 4
%d=20; % mg

% pt 6
d=20; % mg

% pt 8
%d=40; % mg

% pt 21
%d=20; % mg

% pt 3
dn_total=62;
dn_taken=60;

% pt 4
dn_total=90;
dn_taken=56;

% pt 6
dn_total=90;
dn_taken=90;

% pt 8
dn_total=90;
dn_taken=90;

% pt 21
dn_total=101;
dn_taken=93;

krit=4;

TTR_success=0.6;
```
use_perfect=1;

pt=3; % change this according to the patient

options = odeset('RelTol',1e-6);

for ii=1:rep;
    D=[d 0 0];
    start=1;
    time_dose=0;

    init_PKPD_param_omeprazole % call an init_PKPD_param_omeprazole file

    E_baseline_ii=E_baseline(ii);
    H_baseline_ii=H_baseline(ii);
    tlag_ii=tlag(ii);
    v1_ii=v1(ii);
    kb_ii=kb(ii);
    tp_ii=tp(ii);
    ke_ii=ke(ii);
    kdeg_ii=kdeg(ii);
    kd_ii=kd(ii);
    kout_ii=kout(ii);
    km_ii=H_baseline_ii*kout_ii;

    inits = [0 E_baseline_ii H_baseline_ii];

    if use_perfect==1;
        dn_taken=dn_total;
    end

    for jj=1:dn_taken

        if use_perfect==0;
            if pt==3;
                load('di_pt3.mat'); % actual dose interval of pt 3
                di=di_pt3(1,jj);
            end

            if pt==4;
                load('di_pt4.mat'); % actual dose interval of pt 4
                di=di_pt4(1,jj);
            end

            if pt==6;
                load('di_pt6.mat'); % actual dose interval of pt 6
                di=di_pt6(1,jj);
            end

            if pt==8;
                load('di_pt8.mat'); % actual dose interval of pt 8
                di=di_pt8(1,jj);
            end
        end
    end
if pt==21;
load('di_pt21.mat'); % actual dose interval of pt 21
di=di_pt21{1,jj};
end
else
dii=repmat(24,1,dn_taken);
di=dii(1,jj); % dose interval for perfect adherence
end

TT=[0:1:di];
stop=start+length(TT)-1;

inits=inits+D;

sol=ode45(@ode_omeprazole,[0 di],[inits,options,tlag_ii,v1_ii,km_ii,tp_ii,ke_ii,kdeg_ii,kd_ii,kout_ii]);

A3=deval(sol,TT,3);
pH=7-(log10(A3));

inits=deval(sol,di)';

F(ii,start:stop)=pH;
T(ii,start:stop)=TT+time_dose;
start=start+1;
time_dose=time_dose+di;
Trough_pH(jj)=pH(length(TT));
Trough_pH_ss=Trough_pH(21:length(Trough_pH));
end

criterion_omeprazole

plot(T(ii,:)/24,F(ii,:))
xlabel('Time (days)')
ylabel('pH')
xlim([0 70])
ylim([3 6])
set(gca,'xtick',0:10:70)
target = 4;
hline = refline([0 target]);
hline.Color = 'r';
end

overall_success = sum(success_outcome);
overall_success
fractional_overall_success = overall_success / rep

init_PKPD_param_omeprazole

%% Initialising omeprazole PKPD parameters

%% parameter values % group 1 data
tlag=0.5; % h
v1=42.8; % L
ke=0.28; % /h
kdeg=0.04; \% /h
kd=0.13; \% /mcg*L/h
km=15.7; \% mM/h
kb=16.3; \% mM/h
tp=12.5; \% h
kout=0.59; \% /h
E_baseline=1;
HBaseline=10^3.9;

%% BSV 30%
BSV_parPK=[0.09 0 0 0 0; 0 0.09 0 0 0; 0 0 0.09 0 0; 0 0 0 0.09 0; 0 0 0 0.09]
BSV_parPD=[0.09 0 0 0 0 0; 0 0.09 0 0 0 0; 0 0 0.09 0 0 0; 0 0 0 0.09 0 0; 0 0 0 0 0.09]

%% simulation parameters
% simulating PK parameters
parPK=exp([log(tlag) log(v1) log(ke) log(EBaseline) log(HBaseline)]);
tlag=parPK(:,1);
v1=parPK(:,2);
ke=parPK(:,3);
EBaseline=parPK(:,4);
HBaseline=parPK(:,5);

% simulating PD parameters
parPD=exp([log(kdeg) log(kd) log(km) log(kb) log(tp) log(kout)]);
kdeg=parPD(:,1);
kd=parPD(:,2);
km=parPD(:,3);
kb=parPD(:,4);
tp=parPD(:,5);
kout=parPD(:,6);

ODE_omeprazole

function dAdt = ode_omeprazole(t,A,tlag,v1,km,kb,tp,ke,kdeg,kd,kout)
if t<tlag
C=0;
else
C=(A(1)/v1);
end
kin=km;
dAdt=[-ke*A(1)
   kdeg-kdeg*A(2)-kd*C*A(2)
   kin*A(2)-kout*A(3)];

criterion_omeprazole

% criterion for success for atorvastatin
Trough_pH_ss = Trough_pH((20:length(Trough_pH)));  
n_trough = length(Trough_pH_ss);  
success_ind = (Trough_pH_ss > crit);  

success = sum(success_ind);  

fractional_success = success/n_trough;  

if fractional_success >= TTR_success  
   success_outcome(ii)=1;  
else  
   success_outcome(ii)=0;  
end


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