# Personalised warfarin dosing in children after congenital heart surgery using the model-based approach

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To my family

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## Abstract

Oral anticoagulation with warfarin represents a major challenge to successful drug therapy in children. The aims of this study was to investigate the implementation in routine clinical practice, personalised warfarin dosing using a PK/PD model, in children after congenital heart surgery and to explore the experience of patients/parents and health care professionals with managing long-term warfarin treatment as well as their experience with the model-based dosing approach.

The predictive performance of the PK/PD model was first validated using retrospectively collected data from a cohort of 60 children on long-term warfarin treatment. Seventy percent of the predicted doses were ideal with bias of -0.10 and precision of 0.19.

A prospective interventional quantitative study was then conducted in two groups of children. Group 1 included 5 patients who started warfarin treatment for the first time after cardiac surgery. For the case subjects compared to the controls, the median time to achieve the first therapeutic INR values was longer (5 vs 2 days), the median time to stable anticoagulation was shorter (29.0 vs 96.5 days), the median time to over-anticoagulation was longer (15.0 vs 4.0 days), the median percentage of the INR observations within the target range (%ITR) was higher (70% vs 47.4%), the median percentage of time in therapeutic range (%TTR) was higher (83.4% vs 62.3%), the median frequency of INR measurements per month was comparable (5.0 vs 6.3) and the median frequency of dose alterations was also comparable (20.0 vs 21.0).

Group 2 included 26 patients who were established on maintenance warfarin therapy. For the model-based dosing phase compared to the traditional dosing phase, the mean %ITR was 68.82% compared to 67.9% (p=0.84) and the mean %TTR was 85.47% compared to 80.2% (p=0.09). After excluding 5 patients who experienced medical issues during either phases of treatment, the mean %ITR was 71.28% compared to 65.51% (p=0.22) and the median %TTR was 91.8% compared to phase 77.3 % (p=0.03). The median frequency of INR measurements per month was 2.3 compared to 1.9 (p=0.08) and the median frequency of dose alteration was 6.5 compared to 2.5 (p=0.02). Patients with Fontan circulation had significantly higher %TTR during the model-based dosing phase than during the traditional dosing phase after excluding the 5 patients with medical issues (p=0.02).

Semi-structured interviews were conducted with 3 doctors, 2 cardiac liaison nurses and four family representatives. Three thematic areas emerged from the doctors' interviews; 'medical and clinical knowledge', 'INR monitoring' and 'dose decision'. Four thematic areas emerged from the nurses' interviews; 'role of the cardiac liaison nurses in managing warfarin treatment', 'INR monitoring', 'dose decision' and 'adherence to the prescribed regimen'. Three thematic areas emerged from the families' interviews; 'managing warfarin treatment and the coping mechanism', 'warfarin dose decision' and 'adherence to warfarin treatment'. Both doctors and nurses found the new dosing approach useful and acceptable in patients with stable medical condition. Additionally, three of the families favoured that dosing be performed by a professional experienced with warfarin treatment regardless of the method used.

This study has shown that model-based dosing can improve the anticoagulation control of warfarin and hence reduce its adverse events in children after congenital heart surgery. Further work is required to establish the clinical effectiveness and cost-effectiveness of the new dosing approach in this group of children.

## Publications

## Paper

Basma Al-Metwali, Hussain Mulla (2017) Personalised dosing of medicines for children. *The Journal of Pharmacy and Pharmacology*, 69 (5), pp. 514-524.

## Poster presentations

Basma Al-Metwali, Peter Rivers, Larry Goodyer, Hussain Mulla. Management of warfarin dosing in children after congenital heart surgery: Bayesian dose individualization versus traditional approach. Pharmacokinetics UK, Chester, United Kingdom, November 2015.

Basma Al-Metwali, Hussain Mulla, Sanfui Yong, Linda J O'Hare, Shankarnarayana Sadagopan. Personalized warfarin dosing in children after congenital heart surgery: a randomized, prospective, cross-over, pilot study at Glenfield Hospital, Leicester. British Congenital Cardiac Association Annual Meeting. Nottingham, United Kingdom, November 2016.

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Basma Al-Metwali, Linda J O'Hare. Personalised warfarin dosing in children post cardiac surgery. Congenital Cardiac Nurses Association Annual Meeting. Nottingham, United Kingdom, November 2016.

# Table of Contents

**Abstract** ... 1

**Publications** ... 2

**Table of Contents** ... 3

**List of Tables** ... 7

**List of Figures** ... 8

**Chapter 1: Introduction** ... 10

**1.1. Overview** ... 10

**1.1.1. Personalising drug dosing in children using Bayesian forecasting and population PK/PD models** ... 12

**1.1.2. Personalising warfarin dosing in children using Bayesian forecasting and population PK/PD models** ... 14

**1.2. Warfarin** ... 17

**1.2.1. Warfarin history** ... 17

**1.2.2. Pharmacology and monitoring** ... 17

**1.2.3. Pharmacokinetics** ... 19

**1.2.4. Indications for warfarin therapy** ... 20

**1.2.5. Dosing of warfarin in children** ... 25

**1.2.6. Age-related changes in the pharmacokinetics and pharmacodynamics of warfarin in children** ... 25

**1.2.7. Influence of genetic polymorphisms on warfarin PKs and PDs:** ... 32

**1.2.8. Non-pharmacogenetic factors influencing warfarin PK and PD:** ... 37

**1.2.9. Personalising warfarin dosing in children:** ... 40

**1.2.10. Evidence supporting pharmacogenetic-based and model-based warfarin dosing** 50

**1.2.11. Adherence to warfarin therapy in children:** ... 53

**1.2.12. Aim of the research project:** ... 59

**Chapter 2: Methodology** ... 62

**2.1. Introduction** ... 62

**2.2. The Hamberg warfarin PK/PD model and personalised dosing software operation** ... 63

**2.3. Validation of the Hamberg PK/PD model** ... 68

**2.3.1. Aim of the study** ... 68

**2.3.2. Study subjects** ... 68

**2.3.3. Data collection** ... 68

**2.3.4. Assessment of warfarin maintenance dose prediction** ... 68

**2.3.5. Statistical analysis** ..... 69
**2.4. The prospective clinical study** ..... 70
**2.4.1. Aim of the prospective clinical study** ..... 70
**2.4.2. Objectives of the prospective clinical study** ..... 70
**2.4.3. Study design** ..... 70
**2.4.4. Study participants** ..... 72
**2.4.5. Study outcomes** ..... 73
**2.4.6. Rationale for the chosen study outcomes** ..... 74
**2.4.7. Regulatory and ethical considerations** ..... 75
**2.4.8. Study procedures** ..... 76
**2.4.9. Statistical analysis** ..... 82
**2.5. The qualitative study: Exploration of the experience of patients/parents and health care professionals of warfarin treatment and the new dosing approach** ..... 84
**2.5.1. Aim of the qualitative study** ..... 84
**2.5.2. Objectives of the qualitative study** ..... 84
**2.5.3. Study design** ..... 85
**2.5.4. Study participants** ..... 85
**2.5.5. Outcome measures** ..... 86
**2.5.6. Study procedures** ..... 86
**Chapter 3: Validation of the Hamberg PK/PD model** ..... 91
**3.1. Introduction** ..... 91
**3.2. Methodology** ..... 91
**3.3. Results** ..... 92
**3.3.1. Patient characteristics** ..... 92
**3.3.2. Study outcomes** ..... 93
**3.4. Discussion** ..... 98
**Chapter 4: The prospective clinical study: Patients starting warfarin for the first time post-cardiac surgery (Group 1)** ..... 103
**4.1. Introduction** ..... 103
**4.2. Methodology** ..... 104
**4.3. Results** ..... 104
**4.3.1. Patient characteristics** ..... 104
**4.3.2. Study outcomes** ..... 106
**4.4. Discussion** ..... 113

**Chapter 5: The prospective clinical study: Patients maintained on warfarin treatment post-cardiac surgery (Group 2):** ..... 120

**5.1. Introduction** ..... 120

**5.2. Methodology** ..... 120

**5.3. Results** ..... 121

**5.3.1. Patient characteristics** ..... 121

**5.3.2. Study outcomes** ..... 121

**5.4. Discussion** ..... 140

**Chapter 6: The qualitative study: Exploration of the experience of patients/parents and health care professionals of warfarin treatment and the new dosing approach** ..... 155

**6.1. Introduction** ..... 155

**6.2. Methodology** ..... 156

**6.3. Results** ..... 156

**6.3.1. Doctors' experience with managing warfarin therapy post cardiac surgery** .. 157

**6.3.2. Nurses' experience with managing warfarin therapy post cardiac surgery** .... 168

**6.3.3. Families' experience with managing warfarin therapy post cardiac surgery** . 175

**6.3.4. The experience of the doctors with the model-based warfarin treatment** ..... 190

**6.3.5. The experience of the cardiac liaison nurses with the model-based warfarin treatment** ..... 192

**6.3.6. The experience of the families with the model-based warfarin treatment** ..... 194

**6.4. Discussion** ..... 196

**Chapter 7: General Discussion** ..... 206

**7.1. Advantages and drawbacks of the application of the PK/PD model in clinical practice** ..... 214

**7.2. Necessary steps to enhance the implementation of the PK/PD model in clinical practice** ..... 215

**7.3. Recommendations for future research** ..... 216

**7.4. Conclusions** ..... 217

**References:** ..... 218

**Appendices** ..... 236

**Appendix 1: East Midlands Congenital Heart Centre guidelines for paediatric warfarin dosing** ..... 237

**Appendix 2: Ethical approval letters** ..... 238

**Appendix 3: Consent and assent forms** ..... 247

**Appendix 4: Rounding of Predicted warfarin doses** ..... 252

**Appendix 5: Topic guides for interviews** ..... 254

**Appendix 6: Coding of interviews** ..... 257
**Appendix 7: Transcripts of the interviews** ..... 266
**Appendix 8: The study timeline** ..... 361

# List of Tables

**TABLE 1.** CYP2C9 ALLELE FREQUENCY IN DIFFERENT ETHNIC GROUPS.† ..... 33
**TABLE 2.** CHARACTERISTICS AND MAJOR FINDINGS OF STUDIES CONDUCTED IN CHILDREN TO EVALUATE THE INFLUENCE OF CYP2C9 AND VKORC1 GENETIC POLYMORPHISMS ON WARFARIN ANTICOAGULATION. ..... 38
**TABLE 3.** CHARACTERISTICS OF CHILDREN INVOLVED IN THE DEVELOPMENT OF THE LINEAR REGRESSION MODELS. ..... 43
**TABLE 4.** LINEAR REGRESSION MODELS AND THE FACTORS DESCRIBING PERCENTAGE VARIABILITY IN WARFARIN MAINTENANCE DOSE REQUIREMENTS IN CHILDREN. ..... 44
**TABLE 5.** CHARACTERISTICS OF PAEDIATRIC PATIENTS INCLUDED IN THE EVALUATION OF THE HAMBERG MODEL. ..... 92
**TABLE 6.** RESULTS OF THE VALIDATION OF THE HAMBERG MODEL ON A COHORT OF 60 CHILDREN AFTER CONGENITAL HEART SURGERY AT THE EMCHC. ..... 93
**TABLE 7.** DESCRIPTIVE STATISTICS AND P-VALUES OF THE EFFECT OF DEMOGRAPHIC AND CLINICAL VARIABLES ON WARFARIN DOSE. ..... 96
**TABLE 8.** CHARACTERISTICS OF THE CASE AND CONTROL PATIENTS. ..... 105
**TABLE 9.** RESULTS OF THE STUDY OUTCOMES FOR GROUP 1 CASE AND CONTROL SUBJECTS. 107
**TABLE 10.** DESCRIPTIVE STATISTICS OF THE STUDY OUTCOMES FOR GROUP 1 CASE AND CONTROL SUBJECTS. ..... 108
**TABLE 11.** CHARACTERISTICS OF GROUP 2 PATIENTS. ..... 122
**TABLE 12.** TIME IN THERAPEUTIC RANGE (MEASURED AS %ITR AND %TTR), FREQUENCY OF INR MEASUREMENTS AND FREQUENCY OF DOSE ALTERATIONS OF GROUP 2 PATIENTS. . 123
**TABLE 13.** THE TIME IN THERAPEUTIC RANGE EXPRESSED AS %ITR AND %TTR OF THE TWO TREATMENT PHASES FOR THE PATIENTS WITH MEDICAL ISSUES ..... 124
**TABLE 14.** TIME IN THERAPEUTIC RANGE (%ITR AND %TTR) IN GROUP 2 PATIENTS STRATIFIED INTO AGE AND WEIGHT GROUPS. ..... 125
**TABLE 15.** TIME IN THERAPEUTIC RANGE (%ITR AND %TTR) IN GROUP 2 PATIENTS GROUPED ACCORDING TO THE INDICATION OF WARFARIN AND THE TARGET THERAPEUTIC RANGE. 127
**TABLE 16.** TIME IN THERAPEUTIC RANGE (%ITR AND %TTR) IN GROUP 2 PATIENTS GROUPED ACCORDING TO THE CYP2C9 AND VKORC1 GENOTYPES. ..... 130
**TABLE 17.** TIME IN THERAPEUTIC RANGE (%ITR AND %TTR) IN GROUP 2 PATIENTS STRATIFIED ACCORDING TO THE DOSAGE FORM USED. ..... 131
**TABLE 18.** NUMBER OF DOSE ALTERATIONS IN GROUP 2 PATIENTS GROUPED ACCORDING TO THE INDICATION OF WARFARIN AND THE TARGET THERAPEUTIC RANGE. ..... 132
**TABLE 19.** DESCRIPTIVE STATISTICS AND P-VALUES FOR INR ≥4.0 AND ≥5.0 FOR GROUP 2 PATIENTS. ..... 133
**TABLE 20.** OVER-ANTICOAGULATION FOR THE 26 PATIENTS IN GROUP 2 PATIENTS GROUPED ACCORDING TO THE INDICATION OF WARFARIN AND THE TARGET THERAPEUTIC RANGE. 134
**TABLE 21.** DESCRIPTIVE STATISTICS AND P-VALUES OF THE EFFECT OF GENETIC AND NON-GENETIC VARIABLES ON DAILY WARFARIN DOSE (MG/KG/DAY)† ..... 141
**TABLE 22.** DESCRIPTIVE STATISTICS AND P-VALUES OF THE EFFECT OF GENETIC AND NON-GENETIC VARIABLES ON TIME IN THERAPEUTIC RANGE (%ITR AND %TTR) ..... 142
**TABLE 23.** PSEUDONYMS AND DESCRIPTIONS OF THE STUDY PARTICIPANTS. ..... 156

# List of Figures

**FIGURE 1.** WARFARIN MECHANISM OF ACTION. ..... 18
**FIGURE 2**. THE BAYESIAN FORECASTING APPROACH. ..... 47
**FIGURE 3.** DEVELOPMENT OF THE HAMBERG POPULATION MODEL IN CHILDREN FROM PREVIOUS MODELS IN ADULTS. ..... 49
**FIGURE 4.** EXAMPLE OF INITIAL (A PRIORI) DOSE PREDICTION. ..... 64
**FIGURE 5.** EXAMPLE OF DATA INPUT INTO THE MODEL. ..... 65
**FIGURE 6.** EXAMPLE OF INDIVIDUAL PATIENT'S PARAMETER ESTIMATION. ..... 66
**FIGURE 7.** EXAMPLE OF A POSTERIORI (MAINTENANCE) DOSE PREDICTION. ..... 67
**FIGURE 8.** DESIGN OF THE RANDOMISED, OPEN LABEL, TWO-PERIOD, CROSS-OVER STUDY OF GROUP 2 PATIENTS. ..... 72
**FIGURE 9†.** EXAMPLE OF THE GENOTYPING PROCESS OF CYP2C9*2 AND *3 AND VKORC1. . 79
**FIGURE 10†.** EXAMPLE OF MELTING CURVE DATA. ..... 80
**FIGURE 11.** OBSERVED VS MODEL-PREDICTED WARFARIN MAINTENANCE DOSES FOR THE STUDY COHORT. ..... 93
**FIGURE 12.** MODEL-PREDICTED DOSES WERE PLOTTED AGAINST RESIDUAL DOSES CALCULATED AS (OBSERVED DOSE-PREDICTED DOSE). ..... 94
**FIGURE 13.** RELATIONSHIP BETWEEN OBSERVED WARFARIN MAINTENANCE DOSES (MG/KG/DAY) AND AGE. ..... 95
**FIGURE 14.** BOX PLOT SHOWING THE RELATIONSHIP BETWEEN OBSERVED WARFARIN MAINTENANCE DOSES AND AGE. ..... 97
**FIGURE 15.** BOX PLOT SHOWING THE INFLUENCE OF TREATMENT INDICATION ON THE OBSERVED WARFARIN MAINTENANCE DOSES. ..... 97
**FIGURE 16.** BOX PLOT SHOWING THE EFFECT OF TARGET INR RANGE ON THE OBSERVED WARFARIN MAINTENANCE DOSES. ..... 98
**FIGURE 17.** TIME TO FIRST THERAPEUTIC INR AND TIME TO OVER-ANTICOAGULATION IN GROUP 1 CASE AND CONTROL SUBJECTS. ..... 108
**FIGURE 18.** TIME TO STABLE ANTICOAGULATION IN GROUP 1 CASE AND CONTROL SUBJECTS. ..... 109
**FIGURE 19.** THE PERCENTAGE OF INR MEASUREMENTS IN TARGET THERAPEUTIC RANGE (%ITR) AND PERCENTAGE OF TIME IN THERAPEUTIC RANGE (%TTR) FOR GROUP 1 CASE AND CONTROL SUBJECTS. ..... 110
**FIGURE 20.** THE FREQUENCY OF DOSE CHANGES AND THE FREQUENCY OF INR MEASUREMENTS PER MONTH FOR GROUP 1 CASE AND CONTROL SUBJECTS. ..... 111
**FIGURE 21.** OVER-ANTICOAGULATION IN GROUP 1 CASE AND CONTROL SUBJECTS. ..... 111
**FIGURE 22.** FOREST PLOT OF THE TIME IN THERAPEUTIC RANGE OF THE MODEL AND DOCTOR PHASES FOR GROUP 2 PATIENTS. ..... 128
**FIGURE 23.** RELATIONSHIP BETWEEN AVERAGE DAILY WARFARIN DOSE AND AGE ..... 138

# ***Chapter One***

# *Introduction*

# Chapter 1: Introduction

## 1.1. Overview

This thesis focuses on a new approach to personalise warfarin dosing in children. However, before considering warfarin and the challenges encountered in optimising its effects in children, this overview sets out the problems encountered in drug dosing in this population.

Therapeutic doses for most drugs are proposed depending upon population-level information that focus on the typical patient and recommend a standard fixed dose. However, this 'one size fits all' approach to dosing does not in large part account for the inter-individual variability in drug exposure (pharmacokinetics (PK)) and the biological response (pharmacodynamics (PD)). Demographic, genetic, clinical and environmental factors have been found to contribute significantly to this variability resulting in variable responses to drug therapy or susceptibility to adverse drug reactions (Beumer et al., 2014; Hawwa et al., 2008; Roberts et al., 2014). This is most important in drugs with narrow therapeutic ranges where variability can lead to serious toxicity or otherwise treatment failure (Miyakis et al., 2010; Slattery et al., 1997).

In children, drug doses are usually extrapolated linearly from adult doses and adjusted according to age, body weight or body surface area. This approach is simple, easy and does not entail the use of complex dosing algorithms. However, children are in a continuous state of development and maturation that can significantly impact the pharmacokinetics and pharmacodynamics of drugs, and hence, the relationship between dose and age may not necessarily be linear (Cella et al., 2010). Developmental changes in drug absorption, distribution, metabolism and excretion as well as the response to drugs

have been well documented in children (Kearns et al., 2003). The oral absorption and bioavailability of drugs are altered in young children because of age-related changes in the gastrointestinal tract (Lu and Rosenbaum, 2014). Similarly, drug distribution is influenced by age-related changes in body composition and plasma protein binding (van den Anker, Schwab and Kearns, 2011). Moreover, the maturation of the hepatic metabolising enzymes and the renal excretory function affect the elimination of drugs in children (Fernandez et al., 2011). Furthermore, the response to drugs may be affected by age-related differences in drug-receptor interaction (Kearns et al., 2003; Mulla, 2010). Therefore, simple linear extrapolation of adult doses to children may result in inequivalent systemic exposure and/or response in the two populations. In addition, the effect of genetic polymorphisms on the drugs' pharmacokinetics and pharmacodynamics impose an additional source of variability that should be considered in drug dosing (Vear, Stein and Ho, 2013). As a result, understanding the pharmacokinetics and pharmacodynamics of drugs and the factors that contribute to their inter- and intra- individual variability is pivotal in order to optimise drug therapy in children.

An additional important aspect in optimising therapy in children is adherence to the prescribed regimen. With the help of their family, children on drug treatment and especially those on long-term therapy for chronic illnesses, need to adhere to the prescribed regimens to control the underlying disease. This may involve making significant behavioural and lifestyle changes that can affect adherence to the prescribed regimen. There is a range of factors that can affect adherence in children such as age, family factors, the socioeconomic status, disease/treatment regimen and relationship with the healthcare provider (Cheng and Walter, 2006). Therefore, in order to enhance adherence to drug therapy in children, it is important to obtain a thorough understanding

of the health behaviour from the perspective of children/families and health care professionals.

### 1.1.1. Personalising drug dosing in children using Bayesian forecasting and population PK/PD models

The concept of personalised dosing recognises every individual has unique pharmacokinetic and pharmacodynamic characteristics which govern the time course of the drug effect. Therefore, to optimise drug dosing and hence improve treatment response, knowledge of the individual's PK/PD parameters is essential. This is obtained at a more frequent basis at the beginning of treatment and at longer time intervals when the target therapeutic levels are obtained.

Bayesian forecasting is a proactive approach to dose individualisation of drugs with narrow therapeutic ranges that was first introduced by Sheiner *et al*. in 1979. The method utilises population PK/PD models, incorporating significant covariates that explain the inter- and intra-individual variability, to prospectively identify individual's pharmacokinetic and pharmacodynamic parameters and hence individualise dosing (Sheiner et al., 1979). The population models provide a very useful tool to investigate the pharmacokinetics and pharmacodynamics of drugs in children to ensure the safe and effective use of medicines in this population. The models are very useful as they can be used during complex drug dosing regimens, at non-steady state conditions and when only a limited number of concentration measurements is available. Population models were developed to optimise dosing regimens of drugs that present a major challenge in children, for example anticancer drugs, antimicrobials in critically ill patients, and the oral anticoagulant, warfarin (McCune et al., 2014; Felton et al., 2014; Lala et al., 2013).

Population PK/PD models of anticancer drugs can help to identify and quantify the complex pharmacokinetics of these agents and the relationship between pharmacokinetics and pharmacodynamics as well as the influence of pharmacogenetics (Buil-Bruna et al., 2016). In addition, these models can be used to optimise dosing of single-agent as well as combination regimens and identify possible drug interactions with the anticancer agents. In children, these models can assist in describing the wide variability in this population and identifying the covariates that explain this variability to optimise dosing regimens and hence prevent toxicity and treatment failure in this population (Zandvliet et al., 2008). For example, personalising oral busulfan dosing in children has been shown to improve the clinical outcomes, reduced doses in 69% of children, lower incidence of liver toxicity and successful engraftment in all patients (Bleyzac et al., 2001).

Another therapy area where personalised dosing through population models has been proved to improve the clinical outcome is antimicrobial therapy in critically ill children. Such patients frequently have severely altered and marked inter-individual variability in pharmacokinetics (Roberts et al., 2014) that can increase the likelihood of either treatment failure and emergence of antimicrobial resistance due to low systemic exposure or drug toxicity due to high systemic exposure. Individualising vancomycin dosing in children with malignant haematological disease using population modelling was shown to achieve the target therapeutic range significantly better than the fixed dosing method (Zhao et al., 2014). Also, population model-based individualisation of voriconazole treatment was shown to accurately manage therapy in children independently of steady state conditions (Neely et al., 2015).

### 1.1.2. Personalising warfarin dosing in children using Bayesian forecasting and population PK/PD models

Warfarin, the most widely prescribed oral anticoagulant, represents a major challenge to successful therapy in children. The drug is indicated for the long-term prevention of thromboembolism that is mostly associated with underlying disorders like congenital heart disease with or without mechanical prosthetic valves, cancer, renal disorders and long-term total parenteral nutrition (Andrew et al., 1994; Tait et al., 1996). However, warfarin has a narrow therapeutic range and exhibits large inter- and intra-individual variability in its pharmacokinetics and pharmacodynamics which are also influenced by the genetic polymorphisms of the enzymes Cytochrome P450 2C9 (CYP2C9), and vitamin K epoxide reductase (VKOR), respectively (Hamberg et al., 2014). The results from the largest cohort study of 319 children treated with warfarin, has shown that the proportion of International Normalised Ratio (INR) measurements within the target range was only 47% for the range of 2.0-3.0 and 61% for the range of 2.5-3.5 (Streif et al., 1999). This can lead to either under-anticoagulation with subsequent thrombosis or otherwise over-anticoagulation with consequent bleeding. The incidence of major bleeding events was shown to be 0.5% per patient year (Streif et al., 1999), with patients with mechanical heart valves having a higher incidence of up to 4% per patient year (Rao et al., 1989). Therefore, individualising warfarin dosing is essential to optimise its anticoagulant control.

Population PK/PD models of warfarin that incorporate pharmacogenetic variables have been developed to optimise warfarin dosing in children (Hamberg and Wadelius, 2014). These models are mechanistic-based, describing the exposure-response (or PK-PD) relationship and address the inter- and intra-individual variability in warfarin

pharmacokinetics and pharmacodynamics to improve warfarin treatment in children (Hamberg and Wadelius, 2014). A population PK/PD model for warfarin dose individualisation in children was developed by Lala *et al*. (Lala et al., 2013) based on a previous adult model (J. Lee et al., 2009). The model involved a starting dose nomogram based on weight and CYP2C9 and VKORC1 genotypes and a titration scheme for dose adjustment according to the observed INR values. A warfarin dose individualisation kinetic/pharmacodynamic (K/PD) model was also developed in children by Hamberg *et al*. (Hamberg et al., 2013). The model was an extension of a previous K/PD model in adults that describes the relationship between warfarin dose and INR response to overcome the lack of PK data (plasma warfarin concentration) (Hamberg et al., 2010). The predictive performance of the bridged model was evaluated in a cohort of 49 children treated with warfarin. It has been shown that the model was able to predict ideal maintenance doses (within ± 20% of the observed doses) in 41% of patients with the percentage increased to 70% when 3 or more INR observations were available (Hamberg et al., 2013). The paediatric model has subsequently been implemented in a user-friendly, Java-based decision support tool that utilises the patient's age, baseline INR value, target INR range and CYP2C9 and VKORC1 genotypes to predict warfarin dose. The tool can be used for the prediction of both *a priori* (initial) doses and *a posteriori* (maintenance) doses (Hamberg et al., 2015).

In order to optimise warfarin therapy, it is pivotal to personalise its dosing, however, adherence to the prescribed regimen is equally important. As described earlier, warfarin is a narrow therapeutic range drug that requires accurate dosing and frequent monitoring of the INR to achieve stable anticoagulation. Furthermore, this drug has many diet- and drug-interactions and can be associated with serious adverse events. Thus, children

receiving lifelong warfarin therapy and their families need to adhere to a lifelong regimen to achieve adequate warfarin anticoagulation and prevent the occurrence of adverse events. This involves taking the prescribed dose and monitoring the INR at set times, restricting vitamin K-containing diet, restricting alcohol intake for teenagers and being cautious about potential drug interactions and physical activities that can predispose to injuries and bleeding are also essential to control warfarin treatment. This can add a significant burden both on the patient and the family which may affect adherence. Therefore, understanding the perspectives and experiences of both children/families and health care providers of managing warfarin therapy is essential to enhance adherence to this drug.

Population models for individualising warfarin dosing in children have been developed and evaluated in children. However, these models were never tested clinically, on a prospective basis to assess their clinical utility. In addition, the lived experience of children/families and health care providers with the process of warfarin dosing/monitoring was not previously investigated. The aim of this research project is to first, validate the Hamberg model using the existing cohort of patients managed by the East Midlands Congenital Heart Centre. Second, to prospectively compare warfarin dose management using the Hamberg model with the traditional, 'trial and error' approach. Thirdly, the project will also explore the views of children/parents and health care providers about the usual warfarin dosing/monitoring process as well as their views about the new warfarin dosing method.

This introductory chapter will discuss the oral anticoagulant, warfarin, its pharmacology and monitoring, pharmacokinetics and clinical use in children. The chapter will also discuss the factors that contribute to the inter- and intra-individual variability in warfarin

pharmacokinetics and pharmacodynamics leading to the variability in its dose requirements. The models developed to identify factors contributing to this variability and personalise its dosing in children will be reviewed. Clinical trials conducted to assess genotype-guided dosing of warfarin in adults and children will be also be reviewed. In addition, adherence in children and the factors contributing to non-adherence in this ppulation will also be discussed.

## 1.2. Warfarin

### 1.2.1. Warfarin history

Warfarin is the most widely prescribed oral anticoagulant for the prevention and treatment of thromboembolic events in the world. In the UK, over 1% of the population and 8% of those aged over 80 years have been estimated to be using warfarin therapy (Pirmohamed, 2006). The story of warfarin's discovery started following an outbreak of fatal internal bleeding in cattle after ingestion of spoiled sweet clover hay in Northern USA and Canada in the 1920s. In 1933, Link and co-workers were able to isolate the active compound which they named dicoumarol (3,3′-methylene-bis[4-hydroxycoumarin]). The group continued working to identify more potent coumarin-based anticoagulants for use as rodenticides which led to the discovery of warfarin. It was first approved as a rodenticide in 1948, afterwards, it was approved for human use in 1954. The name warfarin was made by combining 'WARF' from the first letters of the Wisconsin Alumni Research Foundation with '-arin' from coumarin (LINK, 1959).

### 1.2.2. Pharmacology and monitoring

Warfarin is a vitamin K antagonist that produces its anticoagulant effect by inhibiting the enzyme vitamin K epoxide reductase (VKOR) that is required for the recycling of

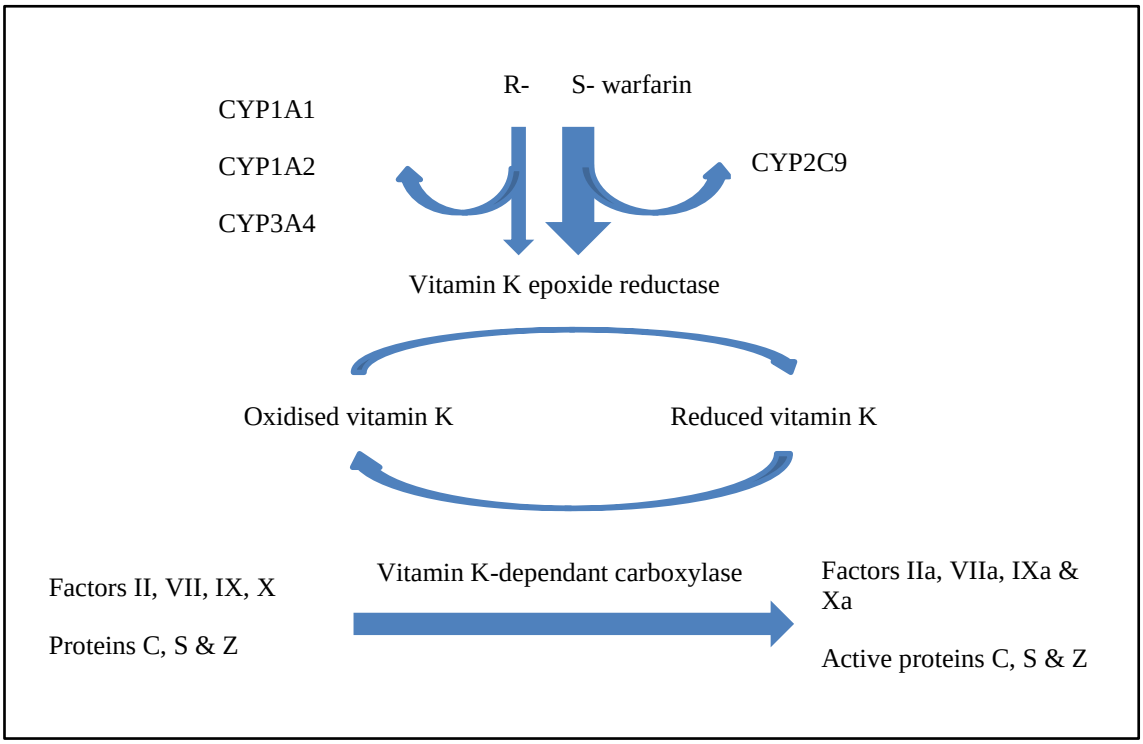


**Figure 1. Warfarin mechanism of action.**

reduced vitamin K, the active form of vitamin K. Reduced vitamin K is a cofactor for the γ-carboxylation of the coagulation factors II, VII, IX and X resulting in the production of inactive forms of these proteins (Figure 1). Warfarin also inhibits the γ-carboxylation of the anticoagulant proteins C, S and Z, consequently, it has a potential procoagulant effect (Ansell et al., 2008).

Monitoring the anticoagulant effect of warfarin is accomplished by measuring the prothrombin time (PT) expressed as the International Normalised Ratio (INR). PT measures the time taken for the blood to clot after the addition of exogenous thromboplastin. The INR is the ratio of the patient's PT and the control PT to the International Sensitivity Index (ISI) which is used to overcome the differences in commercial thromboplastins used in different laboratories (Ronghe, Halsey and Goulden, 2003).

$$INR = (PT_{patient}/PT_{control})^{ISI}$$

The onset of warfarin action depends upon the clearance of the fully carboxylated coagulation factors from the circulation, and hence, their elimination half-lives. The initial changes in PT following the initial dose, and thus the INR, reflect the initial depletion of factor VII which has the shortest half-life (~ 6 hours). Partial anticoagulant effect of warfarin usually develops within two days of treatment initiation. Full antithrombotic effect of warfarin requires up to 6 days of treatment as it is principally dependant on factor II which has the longest elimination half-life of approximately 60 to 72 hours (Hirsh et al., 2003; Wittkowsky, 2003).

### 1.2.3. Pharmacokinetics

After oral administration, warfarin has almost complete bioavailability and peak plasma concentration attainable in 2-8 hours of administration. The rate of dissolution of generic warfarin tablets may vary, which may result in some variation in the rate and extent of absorption. The drug is highly bound (99%) to plasma proteins, mainly albumin (Hogg and Weitz, 2018). Warfarin is available as a racemic mixture of two enantiomers, the S- and the R- isomers, with the S-isomer being about 3 to 5-fold more potent than the R-counterpart. The two isomers undergo hepatic metabolism through different pathways; the S-warfarin is metabolised by Cytochrome P450 2C9 (CYP2C9) while the R- isomer is metabolised by CYP1A1, CYP1A2 and CYP3A4. The half-life ($t_{1/2}$) of warfarin varies between 25 to 60 hours and the duration of action is 2 to 5 days (Hogg and Weitz, 2018).

In children, warfarin pharmacokinetic data are lacking. In a cross-sectional study warfarin was also found to be highly protein bound (about 99%). The mean clearance of S-warfarin (standard deviation SD) was estimated to be 18.1 (9.2) and 12.6 (8.1) ml/min/kg for

children aged 1-11 and 12-18 years, respectively, whereas that of R-warfarin was 4.7 (1.4) and 4.2 (1.6) ml/min/kg for the same age groups, respectively (Takahashi et al., 2000).

### 1.2.4. Indications for warfarin therapy

Warfarin is used for the primary and secondary prevention of thromboembolism in patients with deep venous thrombosis, pulmonary embolism, mechanical prosthetic heart valves, atrial fibrillation and post myocardial infarction (Hirsh et al., 2003). In children, it is also indicated for the prevention of thromboembolism that is mostly associated with underlying disorders like congenital heart disease (CHD) with or without mechanical prosthetic valves, cancer, renal disorders and long-term total parenteral nutrition (Andrew et al., 1994; Tait et al., 1996). The main indication for oral anticoagulation with warfarin in children after cardiac surgery is prophylaxis of thromboembolism after Fontan procedure and mechanical prosthetic valve replacement (Tait et al., 1996). Therefore, these conditions will be discussed in the following sections.

#### 1.2.4.1. The Fontan procedure

Fontan operation is the definitive procedure in a 3-staged palliation for children born with complex congenital cardiac defects such as tricuspid atresia, hypoplastic left heart syndrome and double inlet single ventricle. In such congenital anomalies, 2-ventricle repair cannot be performed resulting in a functionally single ventricle heart. The procedure involves diverting the systemic venous blood directly to the pulmonary arteries without a requirement for pumping by the right ventricle; with the single functioning ventricle working as the left ventricle. The procedure was first introduced by Fontan and Baudet (Fontan and Baudet, 1971). This palliative procedure has led to an increase in the life expectancy of children born with univentricular hearts resulting in an increasing

number entering adulthood. It has been estimated that the UK population having single-ventricle physiology is composed of 1040 adults and 1700 children and the adult number expected to increase by 60% in the next decade (Coats et al., 2014). However, the procedure has been associated with clinically significant sequelae including arrhythmias, systemic ventricular dysfunction, liver dysfunction, protein-losing enteropathy and thromboembolic disease (Giannico et al., 2006; Pundi et al., 2015).

### A- Risk of thromboembolism after the Fontan procedure

Thromboembolic (TE) disease is one of the major complications following Fontan procedure with an incidence ranging from 17 to 33% (Stümper et al., 1991; Fyfe et al., 1991; Balling et al., 2000). TE events can occur in the perioperative period (Todd Tzanetos et al., 2012), immediately post-operatively (McCrindle et al., 2013), during the first post-operative year (Kaulitz et al., 2005) and up to 5 to 10 years postoperatively (Egbe et al., 2016). Thrombotic and embolic events can occur in the venous circulation, the Fontan circuit, intracardiac or in the arterial circulation leading to significant morbidity and mortality. Occlusion of the Fontan circuit by thrombus can result in the failure of the procedure itself. In addition, there are a number of reports about patients developing significant events like pulmonary embolism, myocardial infarction, stroke or cerebrovascular events (Varma et al., 2003; Wilson, Wisheart and Stuart, 1995; Chun et al., 2004; Barker et al., 2005). Moreover, TE disease has been reported to be associated with mortality of up to 25% (Khairy et al., 2008; Monagle et al., 1998).

The slow blood flow resulting from the absence of the ventricular pump, the turbulence occurring in the Fontan circuit and the use of thrombogenic prostheses are all potential risk factors for TE disease (Viswanathan, 2016). Abnormalities in both procoagulant and

anticoagulant proteins have also been well-documented in children with single ventricle palliation. Decreased levels of the procoagulant factors II, V, VII, IX, X and fibrinogen as well as the anticoagulant proteins C and S and antithrombin III were documented after the Fontan procedure. In contrast, levels of factor VIII were shown to be increased after the Fontan palliation contributing to increased risk of thrombosis (Odegard et al., 2003; Odegard et al., 2009; Jahangiri et al., 2000; van Nieuwenhuizen et al., 1999; Goldenberg, Knapp-Clevenger and Manco-Johnson, 2004). Furthermore, endothelial dysfunction in patients with Fontan circulation, as evidenced by increased levels of von Willebrand factor, imposes an additional risk factor for thrombosis (Binotto, Maeda and Lopes, 2008).

**B- Anticoagulant therapy after Fontan procedure**

Considerable controversy exists in the literature with regard to the type of thromboembolism prophylaxis after the Fontan procedure. Some authors recommend oral anticoagulation (Balling et al., 2000; Seipelt et al., 2002; Egbe et al., 2016), while others recommend prophylaxis with aspirin (antiplatelet therapy) (Jacobs et al., 2002). Moreover, a prospective randomised clinical trial conducted by Monagle *et al* and other observational studies found no significant difference between aspirin and warfarin as thromboprophylaxis after the Fontan procedure (Monagle et al., 2011; Potter et al., 2013; Iyengar et al., 2016). Interestingly, a study conducted in adult patients with Fontan circulation has shown that in addition to having increased platelet activity, systemic inflammation, and endothelial dysfunction, a significant number of patients treated with aspirin also experienced aspirin resistance which may have contributed to their increased incidence of TE events (Tomkiewicz-Pajak et al., 2015).

When oral anticoagulation is recommended after the Fontan procedure, warfarin or another vitamin K antagonist (VKA) is usually used to attain a target INR of 2.5 (range 2.0-3.0) (Giglia et al., 2013; Monagle et al., 2012; Patricia Massicotte and Olley Chair, 2005)

#### 1.2.4.2. Mechanical prosthetic heart valves

In children, congenital lesions of the aortic and/or mitral valves may necessitate valve replacement. Valve lesions due to congenital defects account for 5% of valve operations worldwide (Chambers and Bridgewater, 2014). Replacement mechanical valves impose a significant risk of thrombosis and thromboembolism due to alteration of blood flow, surgical disruption of vessel walls and exposure of circulating blood to artificial surfaces (Sun et al., 2009). The annual incidence of TE events in children after mechanical valve replacement receiving no anticoagulation has been estimated to be 5.7% (Sade et al., 1988). The incidence varies with the type and position of the prosthetic valve with older-generation mechanical valves and valves implanted in the mitral position having higher incidence of thrombosis. The risk of TE is highest in the early postoperative period up to one year postoperatively followed by a decrease in TE incidence thereafter. TE complications related to mechanical prostheses are associated with significant morbidity including valve obstruction and systemic emboli. Moreover, obstructive mechanical valve thrombosis has been shown to be associated with up to 10 % mortality (Roudaut, Serri and Lafitte, 2007).

##### 1.2.4.2.1. Anticoagulant therapy after mechanical valve replacement

Children with mechanical heart valves require indefinite oral anticoagulation with a vitamin K antagonist (VKA) to prevent thromboembolism (Giglia et al., 2013). The

intensity of anticoagulation (the target INR value) depends upon the type and the position of the mechanical valve and the presence of TE risk factors (Vahanian et al., 2012; Nishimura et al., 2014). Risk factors for TE include previous TE events, left ventricular dysfunction or hypercoagulable condition (Nishimura et al., 2014). Therefore, anticoagulants should be commenced as early as possible in the first postoperative days, and they are usually bridged with either unfractionated heparin or low molecular weight heparin (Vahanian et al., 2012; Whitlock et al., 2012). Patients with mechanical aortic valve are anticoagulated to a target INR of 2.5 (range 2.0-3.0); with a higher target of 3.0 (range 2.5-3.5) being recommended for patients with risk factors of TE or having older-generation valves in place (Vahanian et al., 2012; Nishimura et al., 2014). The target INR for patients with mechanical mitral valves is also 3.0 (range 2.5-3.5) (Nishimura et al., 2014; Whitlock et al., 2012), however, higher target INR of 3.5 or 4.0 may be recommended for highly thrombogenic valves in patients with risk factors of TE (Vahanian et al., 2012; Keeling et al., 2011).

Despite the use of oral anticoagulants in patients with mechanical valves, there is still a potential for TE events in addition to the bleeding risk. TE complications were reported in up to 4% of patients, with a similar rate of bleeding events reported in children with mechanical valves receiving warfarin therapy (Rao et al., 1989). Major bleeding events can be fatal and TE events can lead to life-threatening consequences like stroke, pulmonary embolism and organ failure. Therefore, accurate dosing of warfarin to avoid over- and under-anticoagulation is required in children to prevent these serious adverse events.

### 1.2.5. Dosing of warfarin in children

Various guidelines have been established to help clinicians calculate the loading and maintenance doses of warfarin. The British National Formulary for Children (BNFC) recommends commencing warfarin therapy for children with a dose of 0.2 mg/kg/day with subsequent doses adjusted per INR measurements and the usual maintenance dose is 0.1-0.3 mg/kg once daily (Monagle et al., 2012; Paediatric Formulary Committee., 2016). The American College of Chest Physicians (ACCP) guidelines recommend an initial dose of 0.2 mg/kg in the first day and dose adjustments are made according to an INR nomogram afterward (Monagle et al., 2012). A lower starting dose of 0.1 mg/kg/day is recommended for patients after the Fontan procedure (Giglia et al., 2013).

However, these guidelines are more general and do not consider the individual patient characteristics and factors that affect warfarin pharmacokinetics (PK) and pharmacodynamics (PD). There is large inter-individual variability in warfarin dose requirements in children where daily maintenance doses can vary from 0.5 to 12.5 mg (Biss et al., 2012). Demographic, genetic, clinical and environmental factors have been shown to contribute considerably to the inter-individual variability in the PK and the PD of warfarin and hence influence the degree of anticoagulation.

### 1.2.6. Age-related changes in the pharmacokinetics and pharmacodynamics of warfarin in children

Children are in a continuous state of development and maturation which can have a significant impact on the drugs' PK and/or PD. These are referred to as developmental pharmacokinetics and developmental pharmacodynamics, respectively. These developmental changes in PK and/or PD can predispose to either supra-therapeutic

exposure and/or response to the drug resulting in serious toxicity or sub-therapeutic exposure and/or response to the drug resulting in treatment failure.

#### 1.2.6.1. Developmental pharmacokinetics

PK in very simple terms describes what the body does to the drug and it includes absorption, distribution, metabolism and elimination.

**A- Absorption**

Age-related changes in the gastrointestinal tract have a significant impact on both the rate and the extent of oral drug absorption and hence bioavailability. Gastric pH, as reported in review articles, is neutral at birth (pH 6-8) then it falls to 1-3 during the first 24-48 hours (Lu and Rosenbaum, 2014). It returns to neutral at 8-10 days and starts to decline slowly afterwards until reaching adult values at the age of 2-3 years (Fernandez et al., 2011; Lu and Rosenbaum, 2014; Matalová, Urbánek and Anzenbacher, 2016). This is closely correlated with the maturation of the gastric mucosa and the gastric pH is further affected by the relatively alkaline milk consumed by the infant (Koren, 1997). This overview has been contradicted by other authors who claimed that gastric pH is comparable in children of all ages and adults and attributed the high gastric pH in the younger infants to the buffering effects of milk (Mooij et al., 2012). This elevated gastric pH can increase the bioavailability of acid-labile drugs such as beta-lactam antibiotics and reduce the bioavailability of weak basic drugs such as phenytoin and phenobarbital (Lu and Rosenbaum, 2014). Alternatively, intestinal pH has been reported to be similar in children and adults, although data on intestinal pH in infants less than two years of age is lacking (Kaye, 2011).

In addition, gastric emptying is thought to be delayed immediately after birth and approaches adult values after 6-8 months (Bowles et al., 2010; Debotton and Dahan, 2014; Fernandez et al., 2011; Matalová, Urbánek and Anzenbacher, 2016). This is anticipated to decrease the rate of absorption of drugs where the rate limiting is gastric emptying, for example paracetamol which was shown to have increased absorption half-life and delayed absorption in neonates infants less than 3 months of age (B. J. Anderson, Woollard and Holford, 2000; B. J. Anderson et al., 2002). In contrast, a model-based meta-analysis of studies in premature neonates through adults has shown that the meal type was the significant covariate for gastric emptying, but not age (Bonner et al., 2015). Similarly, the intestinal transit time is prolonged in neonates as a result of decreased motility and peristalsis, but it is shortened in older infants due to increased intestinal motility (Bartelink et al., 2006). The exact age at which intestinal transit time approaches the adult level is less clear (Bowles et al., 2010).

Immature secretion and activity of bile and pancreatic fluid in the first few months of life causes impaired absorption of fat-soluble vitamins (such as vitamin D and E) and lipophilic compounds (Strolin Benedetti, Whomsley and Baltes, 2005). Moreover, the immaturity of the intestinal drug metabolising enzymes and transport proteins can change the bioavailability of drugs (Lu and Rosenbaum, 2014). Midazolam, for example, was found to have marked decreased oral clearance as a result of the immature intestinal CYP3A4 enzyme which leads to decreased intestinal metabolism of the drug and hence increase in its bioavailability (de Wildt et al., 2002). The oral clearance of gabapentin, in contrast, was found to be higher in children less than 5 years than those older than 5 years or adults as a result of the immature L-amino acid transporter system in the intestinal membrane which causes a reduction in the bioavailability of the drug (Ouellet et al.,

2001). Furthermore, there are other factors that may affect intestinal absorption of drugs like the immaturity of the intestinal mucosa, decreased first-pass metabolism and varying bacterial colonisation (van den Anker, Schwab and Kearns, 2011; Fernandez et al., 2011). Therefore, the absorption of drugs that are affected by the aforementioned factors, and hence their bioavailability, may not approach adult levels until 5 years of age (G. D. Anderson, 2010).

**B- Distribution**

Drug distribution is also subject to the developmental changes occurring particularly in the first year of life. Very young infants have high total body water (80-90% of body weight) reaching adult level of 55-60% by one year of age which affects the distribution of both hydrophilic and lipophilic drugs. In addition, protein binding is also influenced by the ontogeny process where decreased amount and affinity of plasma proteins, albumin and α1-acid glycoprotein has been documented in neonates and young infants (van den Anker, Schwab and Kearns, 2011; Fernandez et al., 2011). This can lead to increased free fraction of the drug available for target interaction as well as clearance.

**C- Metabolism**

Developmental changes in the liver metabolising enzymes affect drug clearance from the body. The most important enzymes involved in drug metabolism, the Cytochrome P450 (CYP 450) isoforms, have low activity at birth and subsequently the activity increases in the first year of life to reach adult values at 1-2 years of age (Fernandez et al., 2011). However, some isoforms, like CYP2C19, may not approach the adult values till more than 10 years of age (Koukouritaki et al., 2004). By the age of 2-3 years, the enzyme activity of specific isoforms of CYP 450, CYP1A2 and CYP3A4, exceed adult

levels; then the activity decreases to adult values by puberty. Therefore, children of this age group require significantly higher weight-adjusted doses of drugs metabolised by these enzymes as compared to adults (G. D. Anderson, 2010). For example, theophylline clearance, which is mainly metabolised by CYP1A2, has been shown to be about 50% above adult values by five years of age and decreases to adult values by 15 years of age (Björkman, 2005).

This linear (weight-adjusted) extrapolation from adult values can underestimate the drug clearance and hence the dose as the relationship between weight and clearance is non-linear. A more accurate estimation can be obtained by allometric scaling of the clearance parameter using a coefficient of 0.75, i.e. $\text{bodyweight}^{0.75}$ is used to scale clearance (B. J. Anderson and Holford, 2008).

The developmental expression of CYP2C9, the enzyme involved in the metabolism of the pharmacologically more potent S-warfarin was investigated (Koukouritaki et al., 2004). The enzyme content and its catalytic activity were found to be 30% of the adult levels in foetal samples in the third trimester of pregnancy. The CYP2C9 protein levels were significantly higher in neonates and infants of 0-5 months of age, however, they were associated with 35-fold inter-individual variation; with 51% of samples showing values proportionate to mature levels. The variability in the protein level and catalytic activity was less pronounced in the age range 5 months to 18 years with most of the samples of 1-2 years possessing the mature protein levels (Koukouritaki et al., 2004).

**D- Elimination**

The renal excretion of drugs is also subject to developmental changes particularly in the first year of life. The glomerular filtration rate (GFR) is low in term neonates, rapidly

increases in the first two weeks of life and then steadily increases to approach the adult level at 8-12 months (van den Anker, Schwab and Kearns, 2011). A model-based analysis of GFR maturation has revealed that GFR approaches half the adult values at 47.7 post-menstrual weeks, whereas at one year of age the GFR was predicted to be 90% of the adult levels (Rhodin et al., 2009). Tubular secretion too is only 20-30% of adult levels at birth and only at around 7-8 months of age approaches adult levels (Hines, 2008).

The impact of developmental changes on warfarin PK has been investigated in a cross-sectional study on prepubertal (age 1-11 years), pubertal (age 12-18 years) and adult (age 37-76 years) patients on long-term warfarin treatment (Takahashi et al., 2000). The mean unbound plasma concentration of S-warfarin was comparable in all age groups. Whereas the body weight-normalised clearance of S-warfarin in the prepubertal group was significantly higher than that in the adult group (18.1 ± 9.2 vs 11.6 ± 5.4 ml/min/kg) and showed a negative correlation with age and high inter-individual variability. The weight-adjusted dose of the prepubertal group was 40% higher than that of the adult group (0.081 vs 0.058 mg/kg/day). However, clearance normalised to estimated liver weight was not different across the three age groups suggesting that liver weight may be a better parameter for estimating warfarin dose in children. In contrast, the pubertal group showed comparable pharmacokinetics to that of the adult group (Takahashi et al., 2000).

#### 1.2.6.2. Developmental pharmacodynamics:

Pharmacodynamics (PD) describes what the drug does to the body and comprises the biological response to the drug. The coagulation system is dynamically evolving and maturing throughout childhood, a process known as developmental haemostasis. At birth, the levels of most of the haemostatic proteins are approximately 50% of the adult levels

and they approach near-adult values by 6 months of life. However, the mean values of most of these proteins are 20% lower than that of adults; which is significantly different, until late teenage years. A similar developmental pattern was observed for the vitamin K-dependant coagulant proteins (II, VII, IX, and X) and the anticoagulant proteins (protein C and protein S), however, protein C and S still have low levels till late teenage years (Andrew et al., 1987; Andrew et al., 1988; Monagle et al., 2006; Andrew et al., 1992; APPEL et al., 2012). The functional maturity of the coagulation system in children under 2 years of age has also been investigated. It was revealed that there were no defects in coagulation and that the haemostatic process is functionally intact even in neonates. However, the study demonstrated that infants of less than 1 year of age can initiate and develop clot faster than adults. The process approaches the adult rate after 1 year of life (Miller et al., 1997). In contrast, the bleeding time upper limit of normal was shown to be longer in the first 10 years of life and approaching the adult level in the teenage years (Andrew et al., 1992).

The effect of developmental changes on warfarin PD in children has also been investigated. It has been shown that the capacity of plasma of children on warfarin treatment to generate thrombin (activated factor II) is decreased and delayed as compared to adults with similar INR values. This is reflected by a significantly lower concentration of prothrombin fragment 1+2 (the endogenous marker for thrombin generation) in children as compared to adults (Massicotte et al., 1998) indicating a higher sensitivity to warfarin in paediatric patients. Takahashi *et al* also investigated the developmental changes in warfarin PD in his study and it was shown that the prepubertal group had significantly lower concentrations of protein C and prothrombin fragment 1+2 and greater

INR and INR/dose ratio suggesting greater response to warfarin in this age group (Takahashi et al., 2000).

### 1.2.7. Influence of genetic polymorphisms on warfarin PKs and PDs:

Genetic polymorphisms of genes that encode for proteins involved in warfarin metabolism and pharmacodynamics have been shown to contribute to the inter-individual variability in warfarin dose requirements and response. Polymorphisms of the gene encoding for CYP2C9 and that encoding for VKOR (vitamin K epoxide reductase complex subunit 1) have been well-established to affect warfarin PK and PD respectively (Takeuchi et al., 2009).

#### 1.2.7.1. Genetic polymorphisms of CYP2C9:

The two most common variant alleles of CYP2C9 that are associated with reduced enzyme activity are CYP2C9*2 (Arg144Cys; rs1799853) and CYP2C9*3 (Ile359Leu; rs1057910) (Rettie et al., 1994; Haining et al., 1996). The CYP2C9*2 and CYP2C9*3 genes encode enzymes that are about 12% and 5% as efficient as the wild-type allele CYP2C9*1, respectively, leading to reduction in the hepatic clearance of warfarin and increase in the plasma concentration of the drug (Zhou, Liu and Chowbay, 2009). The allele frequency of CYP2C9 varies among different ethnic groups (Table 1) (PharmGKB, 2017). As compared to patients with the wild-type (*1/*1) genotype, patients who are heterozygous for CYP2C9*2 and CYP2C9*3 (i.e. *1/*2 and *1/*3) require 19.6% and 33.7% reduction in warfarin dose, respectively (Lindh et al., 2009). In contrast, patients who are homozygous of CYP2C9*2 and CYP2C9*3 (i.e. *2/*2 and *3/*3) require 36% and 78% reduction in warfarin dose, respectively (Lindh et al., 2009). Moreover, those who are compound heterozygotes (i.e. *2/*3) require about 56.7% reduction in dose to

achieve the same level of anticoagulation as those of the wild-type allele (Lindh et al., 2009). In children, Zhang *et al*. conducted a meta-analysis of 8 studies with a total of 507 paediatric patients to assess the influence of CYP2C9 polymorphism on warfarin maintenance dose requirement. The analysis has shown that CYP2C9*1/*2 allele was associated with 15% lower maintenance dose than that of the wild-type (*1/*1), whereas the CYP2C9*1/*3 variant allele was associated with 41% lower maintenance dose. Additionally, warfarin maintenance doses in carriers of CYP2C9 variants which contain at least one variant allele (*2 or *3) were 26% lower than those of the wild-type allele (Zhang et al., 2017).

**Table 1. CYP2C9 allele frequency in different ethnic groups.†**

| CYP2C9 allele | Allele frequency in different ethnic groups (%) | | | | |
|---|---|---|---|---|---|
| | **African** | **African American** | **Caucasian** | **East Asian** | **South/ Central Asian** |
| ***1** | 86.4 | 86.7 | 80 | 96.6 | 78.9 |
| ***2** | 2.4 | 2.3 | 12.6 | 0.06 | 10.7 |
| ***3** | 1 | 1.2 | 7.1 | 3.4 | 10.2 |

† (PharmGKB, 2017)

Additional variant alleles of CYP2C9 that are associated with reduced enzyme activity were found to occur almost exclusively in populations of African ancestry and include CYP2C9*5, CYP2C9*6, CYP2C9*8 and CYP2C9*11 (PharmGKB, 2017). Carriers of these variant alleles were found to require significantly lower warfarin doses than those with the wild type allele, CYP2C9*1 (Cavallari et al., 2010). However, there are no studies to date that have investigated the effect of these variant alleles on warfarin dose requirements in children.

#### 1.2.7.2. Genetic polymorphisms of VKORC1:

Similarly, several polymorphisms have been identified in VKORC1, the gene encoding the enzyme VKOR, and found to be associated with variable warfarin dose requirements. These include -1639G>A (rs9923231), 1173C>T (rs9934438), 2255C>T (rs2359612), 1542G>C (rs8050894) and -4931T>C (rs7196161) (Rieder et al., 2005). The presence of any of these polymorphisms was designated as haplotype A and was shown to be associated with reduced expression of VKOR and lower warfarin dose (Rieder et al., 2005). The wild-type haplotype which is associated with higher dose requirement was designated as B (or G depending on the source of nomenclature) (Rieder et al., 2005). These polymorphisms are in strong linkage disequilibrium which means that they are inherited almost always together and therefore assessment of any of these polymorphisms would be informative about others (Rieder et al., 2005; S. Lee et al., 2006; Mushiroda et al., 2006). The most commonly investigated polymorphism is -1639G>A, with patients having the GG, GA and AA genotypes referred to as high-, intermediate- and low- dose warfarin groups, respectively (Rieder et al., 2005; Yuan et al., 2005; Sconce et al., 2005). Patients with the GA genotype require about 25% lower warfarin dose as compared with those of the GG genotype; whereas those with the AA genotype require about 50% lower dose as compared with the wild-type group (Rieder et al., 2005; Yuan et al., 2005; Sconce et al., 2005; Aquilante et al., 2006; Mushiroda et al., 2006; S. Lee et al., 2006). Similar findings were obtained in children where carriers of the GA and AA genotypes have been shown to require 26% and 50% lower warfarin doses as compared to the GG genotype, respectively (Zhang et al., 2015). The VKORC1 -1639G>A allele frequency also varies among different ethnic/racial populations. The average allele frequency is 88.2% in the East Asian population, 41.2% in Caucasians, 15.3% in the

South/Central Asian population, 12.9% in the Africans and 10.3% in the African Americans (PharmGKB, 2017).

#### 1.2.7.3. Other genetic polymorphisms influencing warfarin dose requirements:

There are other important genetic polymorphisms that were found to be associated with warfarin dose requirements (Johnson et al., 2017). CYP4F2 is an enzyme involved in the metabolism of vitamin K (McDonald et al., 2009). The variant allele of CYP4F2 (Val433Met; rs2108622) is associated with reduced enzyme activity resulting in the accumulation of vitamin K and increased warfarin dose requirement in adults (Caldwell et al., 2008). The effect of CYP4F2 genetic polymorphism on warfarin dose requirement has also been investigated in children. In a study of 37 Japanese children, Hirai *et al*. have shown that genetic polymorphism of CYP4F2 was associated with about 30% increase in warfarin dose requirement (Hirai et al., 2013). In contrast, several other studies have found no effect of this polymorphism on warfarin dose requirement in children (Biss et al., 2012; Hamberg et al., 2014; Moreau et al., 2012; Shaw et al., 2014; Wakamiya et al., 2016).

Additionally, a novel genetic polymorphism in the CYP2C enzyme, CYP2Crs12777823, has been identified in African-American adults. Carriers of this variant allele were found to require reduced warfarin doses (Perera et al., 2013). Yet, there are no studies confirming the effect of this genetic polymorphism on warfarin dose requirement in children.

#### 1.2.7.4. The clinical significance of the CYP2C9 and VKORC1 genetic polymorphisms on anticoagulation with warfarin:

The influence of genetic polymorphisms of CYP2C9 and VKORC1 on anticoagulation with warfarin has been extensively investigated in adults particularly during initiation of warfarin therapy (Jorgensen et al., 2012). Possession of variant alleles of CYP2C9 and/or VKORC1 was shown to be associated with shorter time to therapeutic INR, longer time to stable dose, higher frequency of dosage adjustments, increased number of above-range INR values, less time in target therapeutic range, increased risk of over anticoagulation (INR>4.0) and increased risk of bleeding complications during the first 30-90 days of treatment initiation (Limdi et al., 2009; Ozer et al., 2010; Gaikwad et al., 2013; Mega et al., 2015). Some investigators have shown the predominant effects of the variant allele of VKORC1 during the initiation phase (Lund et al., 2012); whereas others have demonstrated that variant alleles of CYP2C9 (particularly CYP2C9*3) have the predominant effects on warfarin anticoagulation during initiation (Meckley et al., 2008; Ma et al., 2012; Mega et al., 2015). The associated higher risk of bleeding complications with variant alleles of CYP2C9 and/or VKORC1 was not only shown during the initiation phase of warfarin therapy but also during the maintenance phase. Carriers of variant alleles of CYP2C9 and/or VKORC1 were shown to be at increased risk of major bleeding complications during initiation, stabilisation and all nonstable periods of anticoagulation with warfarin (Limdi et al., 2008; Tomek et al., 2013).

In contrast, fewer studies were conducted in children to address the clinical significance of CYP2C9 and VKORC1 polymorphisms in children during initiation of warfarin treatment. Details of these studies' populations and findings are demonstrated in Table 2. Carriers of variant alleles of CYP2C9 or VKORC1 have been shown to attain the target

INR range sooner than those with the wild type (Ruud et al., 2008; Shaw et al., 2014). In addition, carriers of variant alleles of VKORC1 have also been shown to have shorter time to over-anticoagulation (INR>4.0) (Shaw et al., 2014). Moreover, carriers of CYP2C9 variant allele have been shown to have more frequent INR values above the target range than those of the wild type (Ruud et al., 2008; BISS et al., 2013; Hawcutt et al., 2014). Furthermore, possession of VKORC1 variant allele and CYP2C9*3 variant allele has been shown to be associated with increased risk of minor and major bleeding events, respectively (Hawcutt et al., 2014; Shaw et al., 2014). Interestingly, possession of variant allele of VKORC1 has been shown to be associated with greater time spent in the target therapeutic range in the first 6 months of therapy (Hawcutt et al., 2014).

### 1.2.8. Non-pharmacogenetic factors influencing warfarin PK and PD:

There are other factors that can have a significant effect on warfarin PK and PD in children. Inter-current illnesses like infections, diarrhoea and vomiting commonly occur at high frequency in children. The complex underlying medical conditions, for instance CHD, may have a considerable impact on warfarin absorption and metabolism (Monagle, Newall and Campbell, 2010).

Additionally, concurrent use of medications, whether for short- or long-term, may result in PK or PD interactions with warfarin. PK interactions include altered absorption, induction or inhibition of metabolism and displacement from plasma protein binding sites; whereas PD interactions include antagonising or potentiating the pharmacological response to warfarin. Examples of drugs that enhance warfarin effect and increase the INR include amiodarone, cimetidine, cotrimoxazole, fluconazole and metronidazole

**Table 2. Characteristics and major findings of studies conducted in children to evaluate the influence of CYP2C9 and VKORC1 genetic polymorphisms on warfarin anticoagulation.**

| Reference | N | Male/female (n) | Age, median (range), year | Ethnicity (%) | Indication | CYP2C9 genotype (%) | VKORC1 genotype (%) | Findings |
|---|---|---|---|---|---|---|---|---|
| **Ruud *et al.* 2008** | 62 (29 on warfarin) | Not reported | 7.3 (mean) 1-14 | Not reported | Cancer | Wild type (72.4)<br>Heterozygous (24.1)<br>Compound heterozygous (3.5) | Not tested | Children with heterozygous CYP2C9 genotype attained the target INR sooner and had more frequent above-range INR values than those with the wild type. |
| **Biss *et al.* 2013** | 51 | 39/12 | 4 (1-17) | Caucasian (64.7) | Cardiac | *1/*1 (68.6)<br>*1/*2 (11.8)<br>*1/*3 (17.6)<br>*2/*3 (2) | -1639G/G (37.3)<br>-1639G/A (51)<br>-1639A/A (11.8) | - CYP2C9 variant allele carriers and VKORC1 AA allele carriers had significantly higher mean peak INR during the first week of therapy.<br>- CYP2C9 variant allele carriers had significantly higher proportion of above-range INR values in the first month of therapy.<br>- VKORC1 AA allele carriers had higher proportion of above-range INR values in the first month of therapy (not statistically significant). |
| **Hawcutt *et al.* 2014** | 100 (97 included in analysis) | 55/45 | 2.3 | European Caucasian (100) | Mostly cardiac | *1/*1 (62.9)<br>*1/*2 (16.5)<br>*1/*3 (15.4)<br>*2/*2 (2.1)<br>*2/*3 (3.1) | -1639G/G (41.2)<br>-1639G/A (46.4)<br>-1639A/A (12.4) | - VKORC1 variant allele associated with greater time in therapeutic range in the first 6 months of therapy.<br>- CYP2C9*2 variant allele associated with higher proportion of above-range INR values in the first week of therapy.<br>- VKORC1 variant allele associated with increased chance of minor bleeding complications. |
| **Shaw *et al.* 2014** | 93 | 52/41 | 4.8 (2 months-17.8) | European (65.6)<br>Asian (17.2)<br>Other (17.2) | Mostly cardiac | *1/*1 (69.9)<br>*1/*2 (15)<br>*1/*3 (12.9)<br>*2/*2 (2.2) | -1639G/G (41.9)<br>-1639G/A (39.8)<br>-1639A/A (18.3) | - VKORC1 genotype had shorter time to first therapeutic INR and time to over-anticoagulation.<br>- CYP2C9*3 genotype had significant association with major bleeding events. |

through inhibition of warfarin metabolism and aspirin and cephalosporins through potentiating the anticoagulant response to warfarin. Whereas examples of drugs inhibiting warfarin effect and decreasing the INR include cholestyramine that impairs warfarin absorption and barbiturates, carbamazepine, phenytoin and rifampicin that induce warfarin metabolism (Ronghe, Halsey and Goulden, 2003; Greenblatt and von Moltke, 2005). The effect of drug interactions which are due to displacement from plasma protein binding sites is transient and rarely of clinical significance (Greenblatt and von Moltke, 2005).

Furthermore, diet also has a considerable influence on anticoagulation with warfarin. High vitamin K-containing diet antagonises the anticoagulant effect of warfarin resulting in increased dose requirement or even resistance to warfarin. Infant formulas contain vitamin K, hence formula-fed infants tend to be resistant to warfarin as compared to breast-fed infants who are usually more sensitive to it (Greenblatt and von Moltke, 2005; Biss et al., 2011).

Moreover, alcohol consumption by adolescents also affects the anticoagulant effect of warfarin. Acute alcohol intoxication can inhibit the hepatic microsomal system and hence warfarin metabolism and thus potentiate its anticoagulant effect whereas chronic heavy alcohol consumption can stimulate the hepatic enzymes and increase warfarin metabolism resulting in a decrease in its anticoagulant effect (Hansten and Horn, 2008). Therefore, patients are usually advised to restrict alcohol intake to avoid such interactions.

Due to the large number of factors and variables that potentially affect the anticoagulant efficacy of warfarin, dosing in children is intensely challenging. There is large between and within-individual variability in warfarin dosing requirements and

treatment with fixed doses of warfarin has been shown to be associated with large inter-individual variability in response which can affect the quality of anticoagulation. The largest cohort study of 319 children treated with warfarin has shown that the proportion of INR measurements within the target range was only 47% for the range of 2.0-3.0 and 61% for the range of 2.5-3.5 (Streif et al., 1999). For a narrow therapeutic range drug like warfarin, this can result in either under-anticoagulation with subsequent thrombosis or otherwise over-anticoagulation with consequent bleeding. The incidence of major bleeding events was shown to be 0.5% per patient year (Streif et al., 1999), with patients with mechanical heart valves having a higher incidence of up to 4% per patient year (Rao et al., 1989) due to the more intense level of anticoagulation required. Therefore, to improve the anticoagulation control of warfarin, it is very important to personalise its dosing by understanding the drug's pharmacokinetics and pharmacodynamics and the factors that contribute to its inter- and intra-individual variability.

### 1.2.9. Personalising warfarin dosing in children:

The current, conventional approach to dosing warfarin in children is to initiate doses according to the standard guidelines and then to individualise by adjusting doses incrementally according to the INR observations (Monagle et al., 2012; Paediatric Formulary Committee., 2016). However, this 'one-size-fits-all' approach results in sub-optimal anticoagulation control and imposes the risk of over- or under-anticoagulation (Streif et al., 1999). For this reason, attempts have been made to develop models for warfarin dose prediction by considering the demographic and pharmacogenomic factors affecting inter-individual variation in an attempt to personalise (individualise) warfarin dosing in children.

#### 1.2.9.1. Warfarin dose prediction models:

Due to the substantial impact of genetic, demographic, clinical and environmental factors on warfarin dose requirements (see sections 1.2.6 – 1.2.8), various attempts were made to develop dose prediction models that incorporate these factors in order to individualise warfarin therapy (Eriksson and Wadelius, 2012). Warfarin dose prediction models fall into two categories; linear regression models which are based on multiple linear regression analysis and pharmacokinetic/ pharmacodynamic-based (PK/PD-based) models which are mechanism-based models (Hamberg and Wadelius, 2014).

**A- Linear regression models:**

Many studies have been conducted in adults to assess the effect of genetic, demographic and clinical factors on inter-individual variability of warfarin maintenance dose (Gage et al., 2008; Klein et al., 2009). Linear regression analysis was used in these studies to associate these factors with stable warfarin doses and the output was represented by equations to predict warfarin maintenance doses in adults. These pharmacogenetic-based models explained up to 54% of the variability in warfarin maintenance dose requirements (Gage et al., 2008).

Similarly, several studies were conducted in children to assess the effect of these factors on warfarin maintenance dose variability (Nowak-Göttl et al., 2010; Kato et al., 2011; Biss et al., 2012; Moreau et al., 2012; Nguyen et al., 2013; Kamal El-Din et al., 2014; Shaw et al., 2014; Vear et al., 2014; Wakamiya et al., 2016). The output of these models was also represented by equations to estimate warfarin maintenance doses in children. The characteristics of children involved in these studies are summarised in Table 3 and

details of the predictors of warfarin dose variability assessed in each study together with the final equations are summarised in Table 4.

The number of patients included in these investigations ranged from 37 to 120. The models derived from these studies explained 38% (Nowak-Göttl et al., 2010) to 82% (Nguyen et al., 2013) of the variability in warfarin maintenance dose requirements in children. Genetic polymorphism of CYP2C9 was shown to contribute to 0.4% (Nowak-Göttl et al., 2010) to 12.8% (Biss et al., 2012) of dose variance, whereas genetic polymorphism of VKORC1 was shown to contribute to 3.7% (Nowak-Göttl et al., 2010) to 47% (Nguyen et al., 2013) of the dose variance.

The effect of demographic factors on the variability in warfarin maintenance dose has also been investigated. Age was shown to contribute to 12% (Nguyen et al., 2013) to 31% (Vear et al., 2014) of dose variability whereas weight was shown to contribute to 52.8% of this variability (Shaw et al., 2014). In addition, height was shown to contribute to 29.8% (Biss et al., 2012) to 48.1% (Moreau et al., 2012) of the dose variance. Interestingly, age was found to be the only significant determinant of warfarin dose in one study (Kamal El-Din et al., 2014).

Moreover, the effect of clinical factors on warfarin dose variability has also been investigated. The indication for warfarin treatment was shown to contribute to 2.4% (Shaw et al., 2014) to 3.2% (Biss et al., 2012) of dose variability. In addition, the target INR value was shown to contribute to 4.4% (Moreau et al., 2012) to 18% (Nguyen et al., 2013) of the dose variability.

Linear regression models are a standard approach used to describe the relationship between a dependant variable, in this case warfarin dose, and explanatory variable(s), in

**Table 3. Characteristics of children involved in the development of the linear regression models.**

| | **Nowack-Göttl *et al.* 2010** | **Kato *et al.* 2011** | **Biss *et al.* 2012** | **Moreau *et al.* 2012** | **Nguyen *et al.* 2013** | **Shaw *et al.* 2014** | **Vear *et al.* 2014** | **Kamal El-Din *et al.* 2014** | **Wakamiya *et al.* 2016** |
|---|---|---|---|---|---|---|---|---|---|
| **N** | 59 (34 on warfarin) | 48 | 120 | 118 (83 on warfarin) | 37 | 93 | 100 | 41 | 45 |
| **Sex: Male/Female (n)** | 27/32 | 33/ 15 | 82/38 | 46/37 | 26/11 | 52/41 | 46/54 | 23/18 | 38/7 |
| **Age, median (range), year** | 15 (1-19) | 6.6* (0.4-19.3) | 11 (1-18) | 8.4* (3 months-18) | 9.6* (1.8-18.6) | 4.8 (2 months-17.8) | 12.39 (1.-19.8) | 6.5* | 8.1 (3 months-19.2) |
| **Weight, median (range), kg** | 61 (2.3-101) | 19.7* | Not reported | 29.5* (3.5-81.5) | 37.8* (7.6-95) | Not reported | Not reported | 20.8* | 24.6 (3.8-55.6) |
| **Ethnicity (%)** | White (100) | Japanese (100) | White (75.8) Asian (13.3) Black (5) Other (5.8) | White (>90%) | White (73) African-American (18.9) Asian (8.1) | European (65.6) Asian (17.2) Other (17.2) | White (85) African-American (8) Hispanic (3) Other (3) | Egyptian | Japanese |
| **Indication** | Thrombosis | Cardiac | Mostly cardiac | Cardiac | Cardiac | Mostly cardiac | Mostly thrombosis | Mostly cardiac | Mostly cardiac |
| **CYP2C9 genotype (%)** | | | | | | | | | |
| ***1/*1** | 66.1 | 98 | 70 | 64 | 73 | 69.9 | 67 | 65.9 | 100 |
| ***1/*2** | 18.6 | 0 | 14.2 | † | 19 | 15 | 16 | 12.2 | 0 |
| ***1/*3** | 13.6 | 2 | 14.2 | † | 8 | 12.9 | 9 | 14.6 | 0 |
| ***2/*2** | 1.7 | 0 | 0.8 | † | 0 | 2.2 | 0 | 0 | 0 |
| ***2/*3** | 0 | 0 | 0.8 | † | 0 | 0 | 1 | 4.9 | 0 |
| ***3/*3** | 0 | 0 | 0 | † | 0 | 0 | 0 | 2.4 | 0 |
| **VKORC1 genotype (%)** | | | | | | | | | |
| **-1639G/G or 1173 C/C** | 45.7 | 2§ | 35.8 | 30 | 27§ | 41.9 | 32 | 19.5§ | 0§ |
| **-1639G/A or 1173C/T** | 42.4 | 19§ | 45.8 | 52 | 46§ | 39.8 | 54 | 56.1§ | 17.1§ |
| **-1639A/A or 1173T/T** | 11.9 | 79§ | 18.3 | 18 | 27§ | 18.3 | 10 | 24.4§ | 82.9§ |

* Results reported as mean.
† CYP2C9*2 and *3 heterozygotes, 30.0%, CYP2C9*2 and *3 homozygotes and compound heterozygotes, 6.0%.
§ VKORC1 genotype test for 1173C>T.

**Table 4. Linear regression models and the factors describing percentage variability in warfarin maintenance dose requirements in children.**

| Predictors of dose variability | Nowack-Göttl *et al.*2010[1] | Kato *et al.* 2011[2] | Biss *et al.* 2012[3] | Moreau *et al.* 2012[4] | Nguyen *et al.* 2013[5] | Shaw *et al.* 2014[6] | Vear *et al.* 2014[7] | Wakamiya *et al.* 2016[8] |
|---|---|---|---|---|---|---|---|---|
| **Demographic factors** | | | | | | | | |
| **Age** | 28.3% | NA | | | 12% | | 31% | |
| **Weight** | | NA | | | | 52.8% | | |
| **Height** | | | 29.8% | 48.1% | | | | NA |
| **Genetic factors** | | | | | | | | |
| **CYP2C9 genotype** | 0.4% | | 12.8% | 2% | 5% | 8.9% | 6% | |
| **VKORC1 genotype** | 3.7% | NA | 26.6% | 18.2% | 47% | 12.2% | 13% | 27% |
| **Age*VKORC1** | | | | | | | 3% | |
| **Clinical factors** | | | | | | | | |
| **Indication** | | | 3.2% | | | 2.4% | | |
| **Target INR** | | NA | | 4.4% | 18% | | | |
| **Full model** | | | | | | | | |
| **All predictors** | 38% | | 72.4% | 69.% | 82% | 76.3% | 53% | 78.2% |

[1] √Dose (mg/kg/day) = 0.49 - 0.013 (age) - 0.08 (*VKORC1AA]*) + 0.01 (*VKORC1[GA]*) - 0.02 (*Cyp2C9*).
[2] INR = 1.26 + 6.70 × (dose/weight) × (1 + 0.105 × [age – 6.6]) × $0.523^{VKORC1}$.
[3] √dose (mg/day) = - 0.009 + 0.011 (height) + 0.357 (*VKORC1*) - 0.478 (*CYP2C9*3*) - 0.277 (*CYP2C9*2*) + 0.186 (indication).
[4] Dose (mg/week) = -10.77 + 0.28 x height - 5.44 x number of *VKORC1* variant allele(s) +7.83 (if target INR of 2.5) or 11.52 (if target INR of 3.3) - 3.29 x number of *CYP2C9* variant alleles.
[5] Dose (mg/kg/day) = - 0.090 – 0.00060 x age + 0.11 x VKORC1CC + 0.043 x VKORC1TC + 0.045 x CYP2C9*1*1 + 0.039 x CYP2C9*1*2 + 0.073 x Target INR.
[6] √Dose (mg/day) = 1.711 + 0.014 (weight) - 0.257 (number of VKORC1 variant alleles) - 0.127 (number of CYP2C9*2 alleles) - 0.463 (number of CYP2C9*3 alleles) - 0.161 (indication).
[7] Log dose (mg/day) = 1.098 + 0.027 x Age - 1.124 x $VKORC1_{A/A}$ - 0.733 x $VKORC1_{G/A}$ + 0.345 x $CYP2C9_{WT}$ + 0.031 x (Age x $VKORC1_{A/A}$) + 0.037 x (Age x $VKORC1_{G/A}$).
[8] √Dose = 0.235 + 0.011 x height – 0.3 VKORC1TT genotype.
NA predictor was included in the final model but data on the percentage of contribution to variability is not available.

this case the genetic and/or non-genetic factors that can explain the variability in warfarin dose requirements. The development of the model is relatively rapid and does not require a high level of technical expertise with the output being equations that are easy to implement in dose prediction. However, these models are only empirical and descriptive in nature. They fail to explain the underlying relationship between dose variability and the predictors of this variability. In addition, the data in the model are limited to steady state observations, they do not account for the time delay between drug exposure and

response (Hamberg and Wadelius, 2014). In the case of warfarin, there is a time delay between the drug exposure and the increase in INR value which is dependent on the half-lives of the circulating clotting factors (Wittkowsky, 2003). Moreover, linear regression models are restricted to the population on which they were developed and can only be used for the prediction of warfarin maintenance doses (Hamberg and Wadelius, 2014). Yet, during the initiation of warfarin therapy in children, VKORC1 and CYP2C9 genotypes have been shown to have a significant effect on the anticoagulant response and are associated with increased risk of over-anticoagulation and bleeding events (BISS et al., 2013; Hawcutt et al., 2014). It could therefore be argued that, to successfully personalise warfarin treatment, models should ideally include the prediction of both initial and maintenance doses of warfarin (Eriksson and Wadelius, 2012).

**B- Personalising warfarin dosing using population PK/PD models and Bayesian forecasting:**

Bayesian forecasting is a proactive approach to dose individualisation of drugs with narrow therapeutic ranges that was first introduced by Sheiner *et al*. in 1979. The method utilises population PK/PD models, incorporating significant covariates that explain the inter- and intra-individual variability, to prospectively identify individual's PK and PD parameters and hence individualise dosing (Sheiner et al., 1979).

The population PK/PD models are developed using population PK/PD data that cover all phases of treatment i.e. the initial phase as well as the maintenance phase. The databases required for model development are usually complex and need accurate information about date and timing of drug administration and sample collection as well as information about the amount of drug administered, patients' demographics and laboratory tests. The

population PK/PD models consist of three components: a structural model, a stochastic model and a covariate model.

The *structural model* describes the PK and PD of the drug. It utilises 'fixed effects' parameters like clearance (Cl) and volume of distribution (V) for PK and $E_{max}$ (maximum effect) and $EC_{50}$ (concentration required to produce 50% of maximum effect) for PD. The population values of these parameters are called typical values.

The *stochastic model* describes the extent of the 'random effects' which include the inter-individual and intra-individual variability. This is very important clinically in adjusting the dosing of drugs with narrow therapeutic window and wide variability.

The *covariate model* describes the predictors (or covariates) such as demographic, genetic or clinical factors that explain the variability in PK and PD (Mould and Upton, 2012).

In the first step, an individual patient's PK/PD parameters can be estimated (*a priori*) using the typical PK/PD parameters of the population and the individual patient's covariates (age, weight, genotype. etc.). The parameters can subsequently be refined by taking into consideration the patient's measured drug concentrations taken at any time with no need to attain the steady state. The individual PK/PD parameter estimates are then used to predict subsequent drug dose (*a posteriori*) to achieve the required target concentration. After the first few observed drug concentrations, the individual parameter estimates become patient data driven with less effect from the population parameters (Jelliffe et al., 1993). The Bayesian forecasting approach is illustrated in Figure 2.

The population models provide a very useful tool to investigate the PK and PD of drugs in children to ensure the safe and effective use of medicines in this population. The models are versatile as they can be used during complex drug dosing regimens, at non-steady state conditions and when only a limited number of concentration measurements

is available (Thomson and Whiting, 1992). Moreover, models developed in adults can be extrapolated to children by allometric scaling of body size (weight) and addition of maturation function to account for ontogeny of the renal function and drug metabolising enzymes (B. J. Anderson and Holford, 2008). This can help to overcome the difficulties in conducting clinical trials in children due to the ethical restrictions, limited number of patients and constraints in the number and volume of blood samples to be taken.

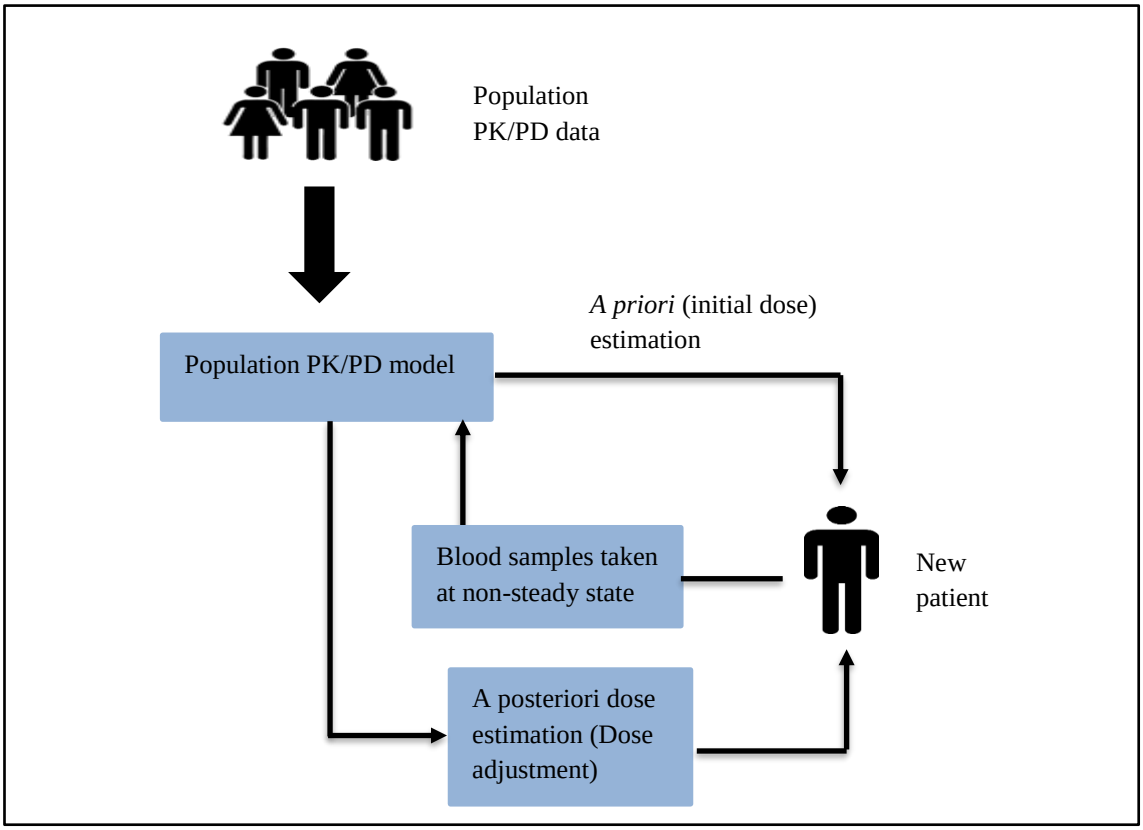


**Figure 2**. The Bayesian forecasting approach. The approach involves developing a population PK/PD model using population PK/PD data. A priori (initial) dose for a new patient is estimated using the mean population PK/PD parameters and the individual patient's covariates (age, weight, etc.). The parameters can subsequently be refined using the individual's drug blood concentrations taken at non-steady state for a posteriori dose estimation (dose adjustment).

Population PK/PD models of warfarin dose prediction incorporating pharmacogenetic variables have been developed and implemented as a tool for Bayesian forecasting. The models describe the exposure-response (or PK-PD) relationship, address the inter- and intra-individual variability in PK and PD and account for the time delay between warfarin exposure and response (increase in INR). In addition, the population models can be extrapolated from one population to another (for instance from adults to children), and can be used for the prediction of initial as well as maintenance doses (Hamberg and Wadelius, 2014). Bridging from adult PK/PD models to children based on pharmacological principles has been used by Hamberg *et al* (Hamberg et al., 2013) and Lala *et al* (Lala et al., 2013). In both instances, parameters from adult PK/PD models were utilised as priors for the derivation of paediatric model by considering the effect of body size on clearance and volume of distribution, the established maturation pattern of warfarin metabolising enzymes and warfarin mechanism of action. Lee and colleagues (2009) utilised a PK/PD model based on the Bayesian approach to aid in optimising warfarin dosing in adults. The model included a starting dose nomogram for initial dose prediction based on CYP2C9 and VKORC1 genotypes, and a titration scheme for maintenance dose revisions based on the measured INR values (J. Lee et al., 2009). The model was used to derive a paediatric PK/PD model which included a starting dose nomogram based on CYP2C9 and VKORC1 genotypes and body weight and a titration scheme for dose adjustments.

Similarly, Hamberg and colleagues developed a population model in adults that was then extrapolated to children (Figure 3).

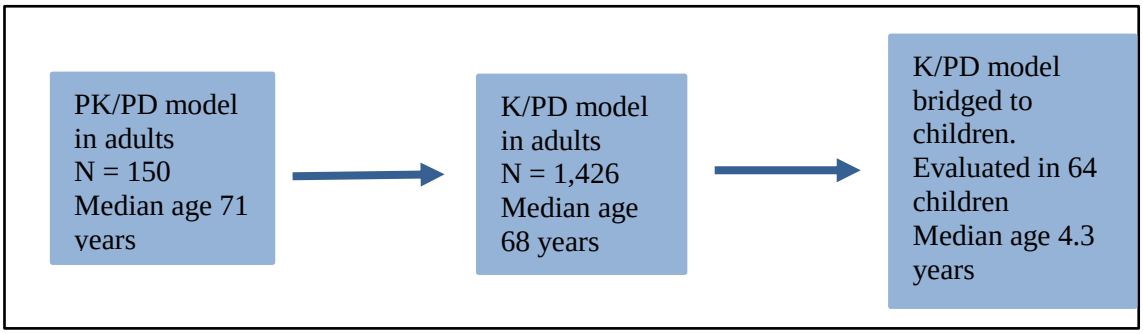


**Figure 3.** Development of the Hamberg population model in children from previous models in adults.

The original adults' PK/PD model was developed using data from 150 patients with a median age of 71 years. Information on S- and R- warfarin plasma concentrations, INR and CYP2C9 and VKORC1 genotypes was used to develop the model. The model accounted for the time delay between warfarin exposure and INR response, and S-warfarin was found to be the only exposure predictor for INR response. Covariates (predictors) for the inter-individual variability in S-warfarin clearance were CYP2C9 genotype and age, whereas VKORC1 was identified as the covariate for the inter-individual variability in warfarin PD ($EC_{50}$). The authors emphasised the importance of taking these covariates into account to improve the individualisation of warfarin therapy during the induction as well as the maintenance phases (Hamberg et al., 2007). This model was then updated using data from 1,426 patients with median age of 68 years. The updated model was a kinetic-pharmacodynamic (K/PD) model that described the relationship between warfarin dose and INR response to overcome the lack of PK data (plasma warfarin concentration) which is not routinely measured. Information on dose, age, INR and CYP2C9 and VKORC1 genotypes were used to develop the model. The model accounted for the time delay between warfarin exposure and INR response and characterised variability in $k_{10}$ (the rate constant which governs the drug elimination) and

$EC_{50}$. Covariates of variability included age and CYP2C9 genotype on clearance (Cl) and VKORC1 genotype on $EC_{50}$. CYP2C9 was found to account for up to a 4.2-fold difference in warfarin maintenance dose, whereas VKORC1 was found to account for up to 2.1-fold difference and age to cause about 6% reduction in dose requirement per decade (Hamberg et al., 2010).

This K/PD model was bridged to children by allometric weight scaling of the clearance and volume of distribution and the addition of a function to account for the ontogeny of the metabolising enzymes. The predictive performance of the bridged model was evaluated in a cohort of 49 children treated with warfarin. It has been shown that the model was able to predict ideal maintenance doses (within ± 20% of the observed doses) in 41% of patients with the percentage increased to 70% when 3 or more INR observations were available (Hamberg et al., 2013). The paediatric model has subsequently been implemented in a user-friendly, Java-based decision support tool that utilises the patient's age, baseline INR value, target INR range and CYP2C9 and VKORC1 genotypes to predict warfarin dose. The tool can be used for the prediction of both *a priori* (initial) doses and *a posteriori* (maintenance) doses (Hamberg et al., 2015). The tool is available free on the website http://www.warfarindoserevision.com.

### 1.2.10. Evidence supporting pharmacogenetic-based and model-based warfarin dosing

Due to the substantial evidence supporting the effect of genetic polymorphisms as well as the clinical and demographic factors on warfarin PK and PD, current guidelines recommend the use of pharmacogenetic-guided dosing algorithms that also incorporate the clinical and demographic determinants of warfarin dose variability when estimating

warfarin doses for both adults and children (Johnson et al., 2017). The Clinical Pharmacogenetics Implementation Consortium guidelines have recommended to use the Biss *et al.* model (Biss et al., 2012) or the Hamberg model (Hamberg et al., 2015) to calculate warfarin dose in children of European ancestry if information about CYP2C9*2 and CYP2C9*3 and VKORC1 genotypes is available (Johnson et al., 2017).

Randomised clinical trials have been conducted in adults to evaluate prospectively the clinical utility of pharmacogenetic-guided dosing of warfarin. The EU-PACT trial involved 455 patients (mean age 67.3 years) starting warfarin therapy for atrial fibrillation (72.1%) or deep venous thrombosis (27.9%) (Pirmohamed et al., 2013). The patients were randomised to either genotype-based warfarin dosing (n=227) or to standard dosing (n=228). The study population was mostly of white ethnicity (more than 98%) and patients were genotyped for CYP2C9*2, CYP2C9*3 and VKORC1. The study has revealed that genotype-based dosing of warfarin has resulted in a higher proportion of time in therapeutic INR range, fewer incidents of over-anticoagulation and shorter time to therapeutic INR than the standard dosing approach (Pirmohamed et al., 2013). Also, a randomised trial (GIFT trial) was conducted to evaluate the safety and effectiveness of genotype-based warfarin dosing as compared with clinical algorithm dosing in orthopaedic patients (Gage et al., 2017). The study recruited a total of 1,650 patients (mean age 72.1 years) who were randomised to either genotype-based dosing (n=831) or clinical algorithm based dosing (n=819). The majority of the study population were of White ethnicity (91%) with only about 6.5% of Black ancestry and about 2% of the Asian ancestry in both arms of the study. The genotypes tested in the study included CYP2C9*2, CYP2C9*3, VKORC1 and CYP4F2. The trial has shown that genotype-based dosing

reduced the risk of major bleeding, INR measurements of 4 or more, venous thromboembolism and death (Gage et al., 2017).

The COAG randomised controlled trial involved 1015 patients who were randomised to either genotype-based dosing (n=514) or clinical algorithm-based dosing (n=501). Twenty seven percent of the study population in each arm were of Black ethnicity. Study participants were genotyped for CYP2C9*2, CYP2C9*3 and VKORC1. The study has shown non-significant difference in the proportion of time in therapeutic INR range between the genotype-based and the clinical algorithms tested in the trial. The proportion of time in target therapeutic range in the Black patients was found to be lower in the genotype-based group than in the clinically-based group (Kimmel et al., 2013). However, it is worth noting that the study did not test the CYP2C9*5, *6, *8 *11 and CYP2Crs12777823 genotypes which are more prevalent in the African American ancestry which may have led to the inaccurate dosing in this group of patients.

PK/PD models have also been assessed prospectively in adults. In a clinical trial conducted by Perlstein *et al*. three different pharmacogenetic-based dosing algorithms of warfarin were developed and prospectively tested (Perlstein et al., 2012). The first algorithm was based on clinical practice guidelines and the published pharmacogenetic data of warfarin. The other two algorithms were PK/PD models based on modelling of dose, INR and genetic and clinical data. All algorithms were prospectively evaluated, and it was shown that the PK/PD models significantly outperformed the clinical algorithm. The proportion of time in target therapeutic range was higher, the proportion of out-of-range INRs was lower, time to first therapeutic INR and stable anticoagulation was shorter in patients treated according to the PK/PD algorithms (Perlstein et al., 2012).

In contrast, only one prospective clinical trial has been conducted in children to evaluate the genotype-guided dosing of warfarin. The study involved 200 Iranian children who started warfarin therapy after cardiac surgery for valve replacement or single ventricle physiology. The study population was divided according to their consent for genotyping into either the genotype-based dosing group (n=50) or the standard dosing group (n=150). The mean age and weight for the genotype-based group and the standard-dosing group was 11.4 versus 11.0 years and 36.8 versus 34.9kg, respectively (Tabib et al., 2015). The algorithm used to predict warfarin doses was the International Warfarin Pharmacogenetics Consortium (IWPC) algorithm (Klein et al., 2009) and doses were adjusted according to body weight, height and body surface area. The study revealed that genotype-guided dosing of warfarin significantly decreased the time to stable dose and hospital stay days but found no difference in time to first therapeutic INR, time to over-anticoagulation and bleeding events (Tabib et al., 2015). Paediatric models were compared where model predicted doses were compared with actual doses administered to children. The Hamberg model was shown to be superior to other models in predicting ideal doses, i.e. predicted doses within 20% of the actual observed doses (Hamberg and Wadelius, 2014; Marek et al., 2016). To date however, there have been no prospectively conducted studies to evaluate the clinical utility of paediatric PK/PD models of warfarin when used in routine clinical practice.

### 1.2.11. Adherence to warfarin therapy in children:

An important aspect in optimising warfarin therapy in children is adherence to the prescribed warfarin regimen. Patients on medical treatment, especially those on long-term therapy for chronic illnesses, are usually asked to follow certain regimens to control the

underlying disease. This may involve making significant behavioural and lifestyle changes that can affect the patient's adherence to the prescribed regimen.

Adherence is defined as the extent of coincidence between a person's behaviour and the medical or health advice in terms of medication, diet or lifestyle. The term compliance was originally used, yet as it implies an asymmetric relationship between the patient and the physician with a more paternalistic role of the latter, hence the terms adherence or concordance are more favoured (Bosworth, Weinberger and Oddone, 2006). Medication non-adherence includes not only taking the medications other than as prescribed and the premature discontinuation of medications but also not starting the prescribed treatment at all (Hugtenburg et al., 2013). Non-adherence to medications can be either unintentional due to for instance forgetfulness to take the medicine or misunderstanding of the provided instructions or intentional especially in patients with chronic diseases who require long-term treatment. Unintentional non-adherence is the most common form of non-adherence in children (Cheng and Walter, 2006).

#### 1.2.11.1. Factors contributing to non-adherence in children:

**1- Age:**

One of the significant determinants of adherence in children is age. Young children are often reliant on their parents' assistance to adhere to take their medications; hence, adherence in this age group is dependent on both the parents and the child. In contrast, adolescence years are associated with increased socialisation, less dependence on the parents and more influence of peers raising the issue of non-adherence (Cheng and Walter, 2006). In a review article of medication adherence in adolescents, the rate of adherence in this population was shown to be around 50% (Staples and Bravender, 2002). In a study of warfarin therapy in children, patients older than 15 years were more likely

to have non-therapeutic INR levels because of omitted doses than any other age group (Newall et al., 2004).

**2- Family factors:**

Family factors are another important determinant of adherence in children. This is of particular importance in children with chronic illness who are required to adhere to a long-term medical regimen that may also need modifications in their lifestyle, for instance diet and physical activity. Adherence to such medical regimens requires the assistance of the family. Parents who are supportive, flexible, engaged, less critical and good at problem resolution can play a pivotal role on their child's adherence to the medical therapy (Fielding and Duff, 1999; Friedrich, Jawad and Miller, 2016). The cohesive family environment and team-based management practices to accommodate the needs of the child's medical regimen into the family daily routines can promote adherence to the prescribed regimen (Friedrich, Jawad and Miller, 2016; Fiese and Everhart, 2006). However, this is more influenced by the child's age where autonomy-seeking adolescents may perceive this support as a threat to their personal freedom leading to poorer adherence (Staples and Bravender, 2002; Fiese and Everhart, 2006). Parents' marital status can also have a significant contribution to children's medical adherence (Fielding and Duff, 1999). Single parenthood and marital conflict were shown to be among the important risk factors of non-adherence in children with cardiac disease (Ittenbach et al., 2009).

**3- The socioeconomic status:**

The socioeconomic status of the family is a further determinant of adherence where families from low socioeconomic groups can face difficulties to adhere to medical and dietary regimens (Fielding and Duff, 1999). Adolescents with type 1 diabetes mellitus

from families from low socioeconomic groups were found to have lower adherence than those from families from upper or middle socioeconomic groups (Pereira et al., 2008).

**4- Adjustment and coping:**

Adjustment and coping of children and families to disease and treatment can also affect adherence. Chronic illnesses usually place children and their families at chronic stress that can cause emotional and behavioural problems and can lead to non-adherence. High levels of coping with stress and adjustment to the diagnosis and treatment is essential to enhance adherence (Compas et al., 2012).

**5- Disease/treatment regimen:**

Adherence can also be affected by the disease and the treatment regimen used. Chronic diseases whose regimens require frequent dosing/monitoring and changes in diet and physical activity can be associated with lower levels of adherence (Cheng and Walter, 2006). Disease duration was found to be one of the predictors of adherence in adolescents with type 1 diabetes (Pereira et al., 2008). These patients were also found to have low adherence rates to diet (15% of patients completely followed the diet advice) and physical exercise (33% of patients followed the advice for physical exercise) (Pereira et al., 2008). In addition, the acceptability of the medicinal product is another critical determinant of adherence. Acceptability is influenced by both patient characteristics, such as age, ability to take the medicinal product and disease state, as well as product characteristics, such as palatability, swallowability, the required dose and dosing frequency and treatment duration (Kozarewicz, 2014). In addition, the acceptability of both patients and health care providers is influenced by the quality of medicine for example the use of generic medicines compared to the brand (Jacomet et al., 2015). Moreover, the cost of treatment is another important determinant of adherence. Treatment price was described as a barrier

to adherence by 12% of adolescents with cystic fibrosis (Dziuban et al., 2010). In addition, treatment cost includes not only the medication cost but also the cost of travelling to perform blood tests required for treatment monitoring. Hospital INR monitoring was dissatisfying to patients and parents because it involved travelling costs, time off school/work and frequent venepuncture (Duggan, Pearce and Guilbert, 2001).

**6- Relationship with the healthcare provider:**

The relationship between the patient/parents and the healthcare provider impacts adherence significantly. Effective communication that involves building a collaborative relationship between the patient/parents and the healthcare provider can significantly enhance adherence to the prescribed regimen, which is particularly important in patients with chronic conditions. This includes close follow-up of patient/parents, establishing a partnership relationship to encourage them to express their beliefs and concerns about the disease and treatment and the barriers to adherence, and providing empathy and education to enhance their satisfaction and adherence to treatment (Brand, Klok and Kaptein, 2013; Croom et al., 2011).

As described earlier, warfarin is a narrow therapeutic range drug that requires accurate dosing and frequent monitoring of the INR to achieve stable anticoagulation. In addition, this drug has many diet- and drug-interactions and can be associated with serious adverse events including bleeding and thrombosis that can further complicate the treatment. For this reason, children with congenital heart disease who are on lifelong warfarin therapy and their families need to adhere to a lifelong regimen to achieve adequate warfarin anticoagulation and prevent the occurrence of adverse events. Adherence to the warfarin regimen involves taking the prescribed dose and monitoring the INR at set times taking into consideration that children often require frequent INR

tests and subsequent dose changes, particularly those below one year of age (Streif et al., 1999). In addition, restricting vitamin K-containing diet, restricting alcohol intake for teenagers and being cautious about potential drug interactions and physical activities that can predispose to injuries and bleeding are also essential to control warfarin treatment. This can add a significant burden both on the patient and the family.

Adherence to warfarin treatment has been investigated in adults. Non-adherence to taking the medication was estimated to be around 21% of patients (Platt et al., 2010). Non-adherence to warfarin, diet or INR monitoring can lead to non-therapeutic INR values and subsequent risk of adverse events. Missed doses, misunderstanding of dosage instructions and consumption of varying amounts of vitamin K-containing diet was found to be the most common cause of out-of-range INR values (Waterman et al., 2004). Non-adherence to INR monitoring was found to result in more than 55% of out-of-range INR values and about 50% increase in the risk of thromboembolism (Witt et al., 2013). Whereas, patients' and healthcare providers' perspectives and experiences with warfarin treatment in adults have been studied (Bajorek et al., 2006; Dantas et al., 2004; Borg Xuereb, Shaw and Lane, 2012; Borg Xuereb, Shaw and Lane, 2016), similar studies of adherence to warfarin in children with congenital heart disease is lacking. Adherence issues in children are different from those in adults; warfarin chronic use in adult population is mostly for older patients who encounter health, behaviour and lifestyle issues that are different from those encountered in children and adolescents.

One study has investigated the impact of warfarin treatment on children with congenital heart disease and their parents focusing mainly on INR monitoring in the hospital (Duggan, Pearce and Guilbert, 2001). Patients/parents expressed their dissatisfaction with hospital monitoring as it involved time off school/work, travelling cost and inconvenience

of venepuncture. The participants were also asked about their experience with long-term warfarin use. Both children and parents expressed their concerns about the risk of bleeding and the responsibility of ensuring regular intake of the medication and keeping the INR within the target therapeutic range (Duggan, Pearce and Guilbert, 2001). Nevertheless, the experience of children/parents with warfarin treatment is still not fully investigated, including the child's/parents' involvement in the dosing/monitoring process. In addition, the health care providers' experience in this process has not been investigated.

Warfarin dose management in children can be intensely challenging because of the many factors discussed earlier. Therefore, attempts have been made to develop models for managing warfarin dose taking into consideration inter- and intra-individual variations. However, these models were never tested clinically on a prospective basis and the models' estimated doses were compared with actual doses administered to patients. The current practice in the East Midlands Congenital Heart Centre, Glenfield Hospital, is to initiate warfarin treatment with loading doses and then to adjust incrementally according to INR observations (Appendix 1) which imposes the risk of fluctuations in doses and INR response. Furthermore, the lived experience of children/ families and health care providers with warfarin dosing/monitoring process has not previously been investigated.

### 1.2.12. Aim of the research project:

The current, traditional approach to dosing warfarin in post-operative cardiac children is to initiate doses according to the BNFC recommendations, and then to individualise by adjusting doses incrementally according to the INR observations. The aims of this research project are to investigate for the first time the implementation, in

routine clinical practice, warfarin dose management using a pharmacokinetic-pharmacodynamic (PK/PD) model and to explore the views of both patients/parents and health care professionals.

#### 1.2.12.1. Validation of the Hamberg model:

To validate the Hamberg PK/PD model for use in the East Midlands Congenital Heart Centre (EMCHC), a retrospective study to assess the accuracy and precision of the model in predicting warfarin maintenance doses will be assessed. The data will be collected from a cohort of post-operative cardiac children on long-term warfarin treatment.

#### 1.2.12.2. Prospective clinical study:

To prospectively compare warfarin dose management in warfarin-naïve and warfarin-established patients using the Hamberg PK/PD model, with the traditional, 'trial and error' approach. All patients will be genotyped for CYP2C9 and VKORC1 polymorphisms.

#### 1.2.12.3. Exploration of Patients/Parents/Health Care Professionals views on warfarin

To explore the lived experience of patients/parents with warfarin dosing/monitoring as well as their experience with the new warfarin dosing model. The health care providers' experience with warfarin dosing/monitoring as well as their experience with the new dosing model will also be investigated.

# Chapter Two

# Methodology

# Chapter 2: Methodology

## 2.1. Introduction

The pharmacogenetic-based warfarin dosing algorithms have, to date, been evaluated using two approaches. The first approach is a retrospective evaluation comparing the algorithm-predicted doses with the actual doses administered to patients on stable therapeutic doses of warfarin (Klein et al., 2009). The second approach involves prospective clinical evaluation in randomised clinical trials of patients starting warfarin for the first time (Kimmel et al., 2013; Pirmohamed et al., 2013). The paediatric warfarin dose prediction models were mostly evaluated using the former approach (Hamberg and Wadelius, 2014; Marek et al., 2016) with only one study evaluating pharmacogenetic-guided warfarin dosing in a prospective clinical trial (Tabib et al., 2015).

This research project can be separated into three parts. The first was a retrospective evaluation of the Hamberg model in a cohort of post-operative cardiac children on long-term warfarin therapy. The second was a prospective evaluation of the model in two groups of post-operative cardiac children. The first group (Group 1) included paediatric patients starting warfarin treatment for the first time post-operative congenital heart surgery. The second group (Group 2) was a sample of children who had already been established on long-term warfarin treatment. In the third and final stage, a subsample of patients, from Group 1 and 2, were selected in order to conduct a qualitative study to explore experience of patients/parents, together with their doctors and nurses who were involved in the regular monitoring and determination of warfarin doses in order to optimise the effectiveness of the medicine and minimise its risks.

## 2.2. The Hamberg warfarin PK/PD model and personalised dosing software operation

Before describing the personalised dosing software operation, it is important to describe 'how best' the model parameters are estimated. Population models that utilise the Bayesian forecasting approach provide parameter estimation based on minimizing the objective function value (OFV) using maximum likelihood estimation. OFV is a number that overall summarises how closely the predicted data match the observations (Mould and Upton, 2013). To describe maximum likelihood estimation, a given set of observed and predicted data values is assumed. The predicted data values are assumed to have a normal distribution with a mean and a standard deviation. The likelihood of the observed data is the deviation of the observed data from the centre of this distribution. OFV is expressed as the negative sum of the log of the likelihoods (Mould and Upton, 2012). Within a particular model, OFV is used to compare parameter values where the lowest OFV is associated with the best fit parameters. OFV can also be used to rank the goodness-of-fit of different models with the same dataset (Mould and Upton, 2012).

As described earlier, the Hamberg PK/PD model (Hamberg et al., 2013), has been implemented in a user-friendly, Java-based decision support tool to predict both initial (*a priori*) and maintenance (*a posteriori*) warfarin doses in children (Hamberg et al., 2015). For initial (*a priori*) dose prediction, data on patient's age, weight, CYP2C9 and VKORC1 genotypes, baseline INR value and target INR range are entered into the corresponding fields in the model (Figure 4). The initial dose is estimated using the typical (mean) parameter estimates of the population and the individual patient's

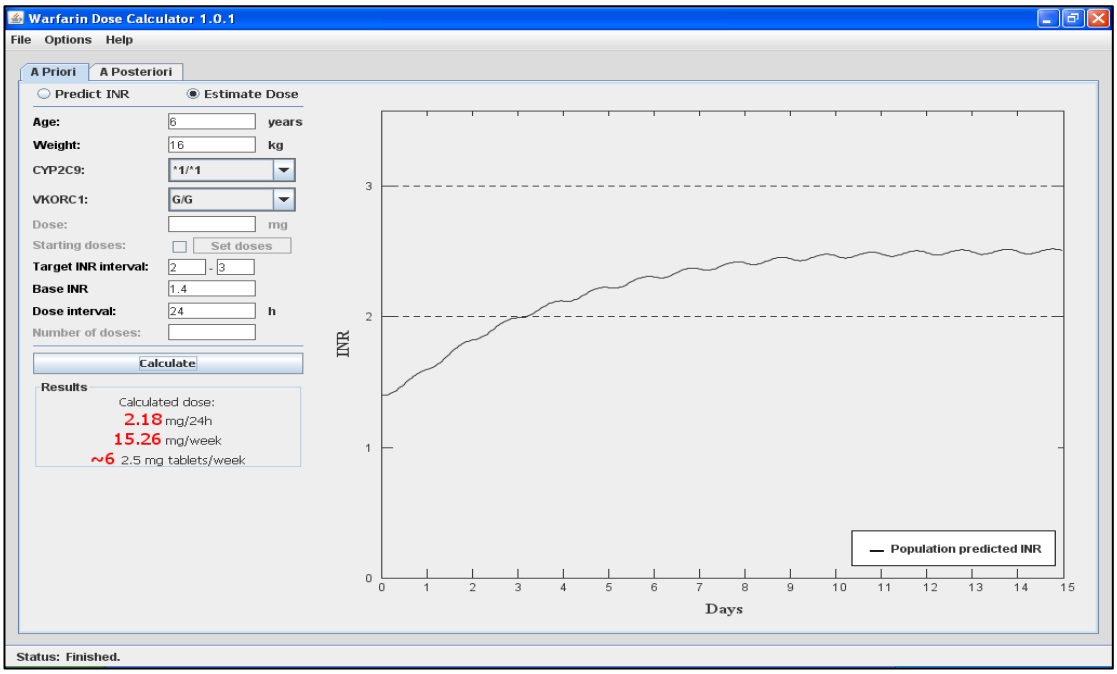


**Figure 4. Example of initial (a priori) dose prediction.** This figure shows an example of initial (a priori) dose prediction of a 6.0-year-old child, with 16-kg bodyweight, CYP2C9*1/*1 and VKORC1 G/G genotypes, target INR range of 2.0-3.0 and baseline INR value of 1.4. The predicted initial dose is 2.18 mg/day, 15.26mg/week. The plot depicts the predicted typical INR curve starting from the first dose until steady state attainment.

covariates (age, weight and CYP2C9 and VKORC1 genotypes). For dose estimation, the tool uses the mean of the target INR range as the target INR. For example, if the target INR range is 2.0-3.0, the tool will use 2.5 as the target INR to estimate the dose (Hamberg et al., 2015). The output is presented as a text field of the predicted *a priori* dose in mg/day and mg/week as well as a plot of the predicted typical INR curve from the first dose until steady state achievement. The plot also depicts the marked target INR range to assist in interpreting the predicted INR curve. The text field also shows the equivalent number of 2.5 mg tablets/week which is an adaptation to Swedish conditions where only 2.5 mg tablets are licensed (Hamberg et al., 2015).

When one or more INR observations are available, the tool can be used to predict the adjusted maintenance dose. The process of predicting the maintenance (*a posteriori*) dose includes two steps. In the first step, each patient's data including demographics, CYP2C9

and VKORC1 genotypes, warfarin doses and the corresponding INR observations and times of dosing and blood sampling for INR tests is entered into the model to estimate individual patient's model parameters (Figure 5).

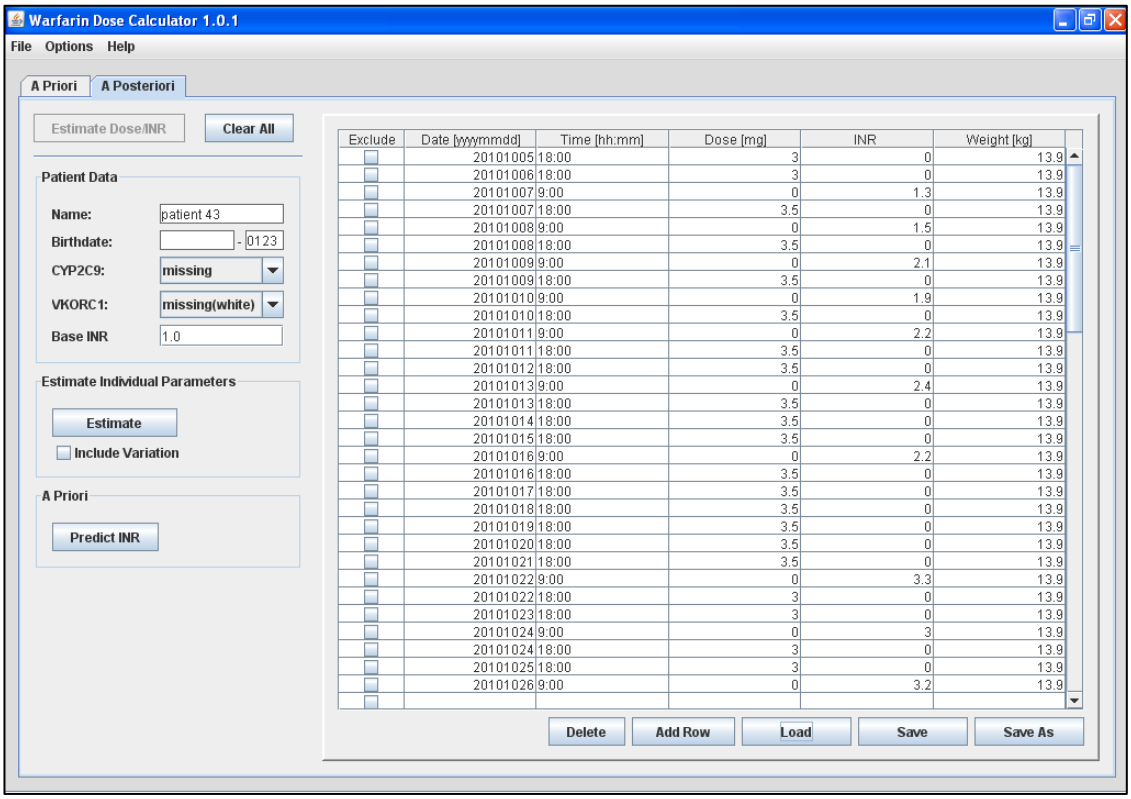


**Figure 5. Example of data input into the model.** The patient's demographic data and data of warfarin dosing, INR observations and timing of dose administration and blood sampling for INR tests are imported from the patient's Excel file. The genotype data of CYP2C9 and VKORC1 are input as "missing" in the related fields as they were not available. The baseline INR value is set at 1.0 for all patients. By pressing the "Estimate" button, the model will estimate the individual parameter estimates of the patient.

The model parameters include $K_{10}$, the rate constant which governs the drug elimination and $EC_{50}$, the concentration required to produce 50% of the maximum effect. When more INR observations are obtained, the individual model parameter estimates are refined and become specific to the individual patient which helps to increase the accuracy and precision of the dose predicted. The individual patients' data can be either entered

manually or imported from individual patients' Excel files that have specific requirements of file naming and data format (Hamberg et al., 2015). If genotype information of CYP2C9 and VKORC1 is not available, it can be entered as "missing" in the corresponding fields in the model. If the baseline INR value is not available, it can be set at the default value of 1.0. The output is presented in a new screen (Figure 6) of two fields; a text field showing the typical (mean) and the individual parameter estimates of $K_{10}$ and $EC_{50}$, and a plot of the predicted INR curves of the population (black curve) and the individual (red curve). The observed INR values of the patient are also shown in the plot which can help to assess the individual fit of the curve.

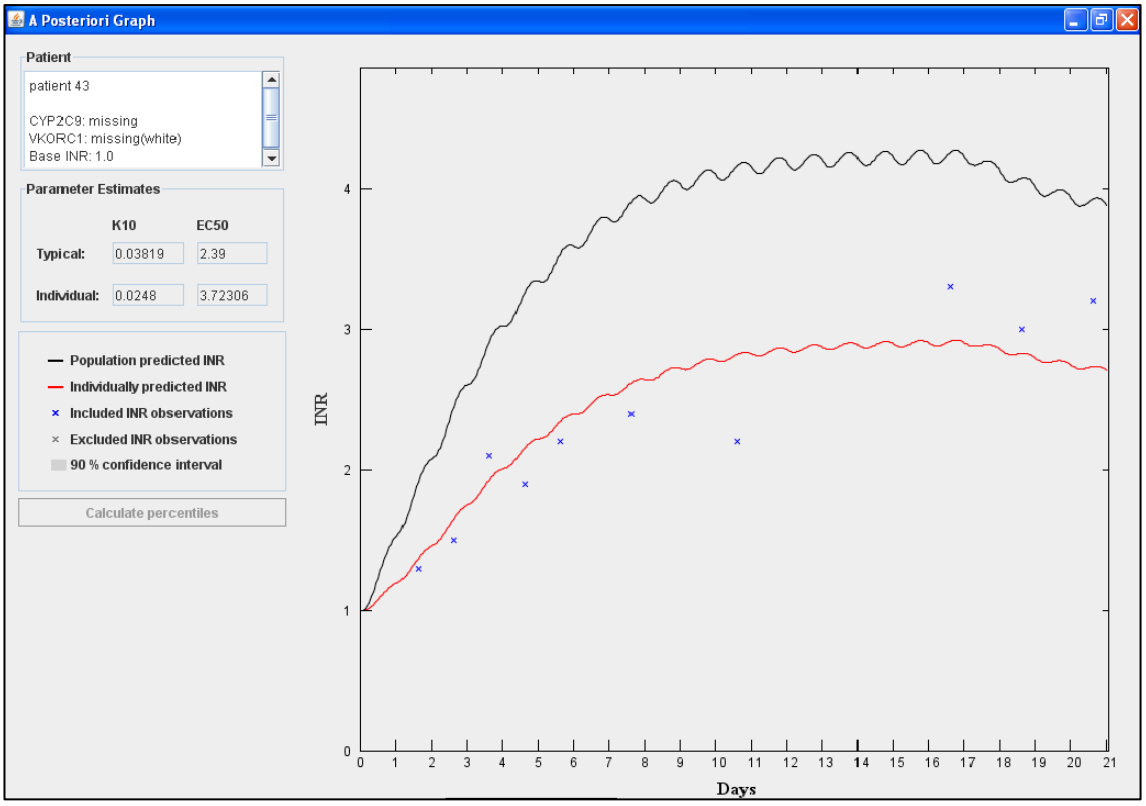


**Figure 6. Example of individual patient's parameter estimation.** The model output shows the typical and individual parameter estimates of K10 and EC50. It also shows the predicted INR curves of the population (black) and the patient (red) as well as the patient's actual IR observations.

In the second step, the individual patient's maintenance dose is predicted utilising the individual patient's parameters (Figure 7). The output is presented as a text field displaying the predicted maintenance dose in mg per day and mg per week as well as the equivalent number of 2.5 mg tablets per week, an adaptation to Swedish conditions where only 2.5 mg tablets are licensed. The output also includes a plot of the patient's predicted INR curve after the administration of the predicted dose and the target therapeutic range of the patient.

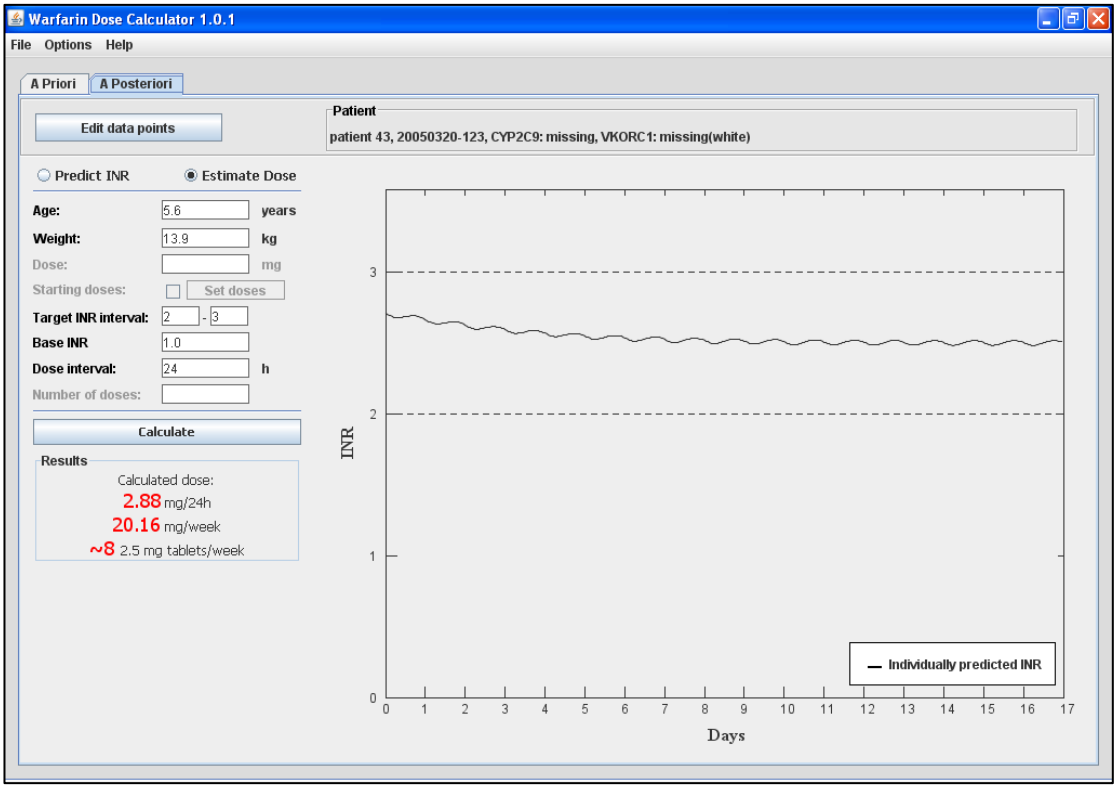


**Figure 7. Example of a posteriori (maintenance) dose prediction.** This figure shows an example of maintenance dose prediction of a 5.6-year-old child, with 13.9 kg body weight, target INR range of 2.0-3.0 and baseline INR value of 1.0. Dose prediction is made using the estimated individual parameters in Figure 4. The predicted maintenance dose is 2.88 mg/day, 20.16 mg/week. The plot depicts the individually predicted INR curve after the administration of the predicted dose (2.88mg).

## 2.3.Validation of the Hamberg PK/PD model

### 2.3.1. Aim of the study

The aim of the study was to validate the use of the Hamberg model in routine clinical practice at the EMCHC by assessing its accuracy and precision in predicting warfarin maintenance doses using retrospectively collected data from an existing cohort of post-operative cardiac children on long-term warfarin treatment.

### 2.3.2. Study subjects

Children below the age of 18 years who were currently receiving warfarin treatment at the EMCHC in Glenfield hospital, Leicester were included in the assessment. Eligible study subjects were identified from the EMCHC database at Glenfield hospital.

### 2.3.3. Data collection

Demography and retrospective, longitudinal warfarin prescription data was collected from the patients' medical records and INR monitoring charts. The data collected included date of birth, gender, ethnicity, weight, indication of warfarin, target INR range, date warfarin started, warfarin doses and the corresponding INR observations.

Ethical approval to use this data was not required because this study was conducted as an audit under the supervision of the clinical supervisor, who is a member of the direct care team, as well as the direct care team.

### 2.3.4. Assessment of warfarin maintenance dose prediction

The Java-based warfarin dosing model version 1.0.1 (Hamberg et al., 2015) was used to predict each individual patient's warfarin maintenance doses that were then compared to the actual doses prescribed by the doctors. The assessment was conducted during the

period children were observed to have stable maintenance warfarin dosing. The period of stable warfarin treatment was defined as at least three consecutive INR measurements in the target therapeutic INR range over a period of at least four weeks with no change in warfarin dose (Hamberg et al., 2013).

Excel files that have specific requirements of file naming and data format (Hamberg et al., 2015) were initiated for each individual patient. These files contained data about patient's weight, warfarin doses and the corresponding INR observations and times of dosing and blood sampling for INR tests from the first day of warfarin therapy up to the first stable treatment period. These data were used for the estimation of individual patient's model parameters and subsequent dose prediction as described in section 2.2. The predicted daily maintenance dose was then compared with the actual observed daily maintenance dose that was prescribed by the doctors. When the prescribed dose was alternating, for e.g. 1 and 1.5 mg, the average daily maintenance dose was used, i.e. 1.25 mg.

### 2.3.5. Statistical analysis

Statistical analysis was conducted using Excel (Microsoft Corp., 2010) and SPSS (IBM Corp., 2013). The demographic and clinical characteristics of the study population were reported descriptively. Model accuracy was evaluated by calculating the difference between model predicted and observed doses, and the results were expressed as prediction error (PE):

$$\mathrm{PE} = \frac{(\text{predicted dose} - \text{observed dose})}{\text{observed dose}}$$

The bias (mean PE) and precision (root mean squared error) were also calculated. Clinical accuracy was evaluated by calculating the percentage of patients in which the model predicted dose was ideal (within 20% of the observed dose), under-predicted (at least 20% below the observed dose) or over-predicted (at least 20% above the observed dose) (Hamberg et al., 2013). The associations between continuous variables and the observed warfarin dose were assessed using Spearman's correlation. The associations between categorical variables and the observed warfarin dose were assessed using Mann-Whitney U test and Kruskal-Wallis test. A p-value of less than 0.05 was considered to be statistically significant.

## 2.4. The prospective clinical study

### 2.4.1. Aim of the prospective clinical study

The aim of the prospective clinical study was to compare warfarin dose management using the Hamberg PK/PD based model with the traditional, 'trial and error' approach.

### 2.4.2. Objectives of the prospective clinical study

The study objectives were first to compare the performance of the Hamberg PK/PD warfarin model estimated dosing with the traditional 'trial and error', protocol guided-adjustments approach to dosing in post-operative cardiac surgical children. The second study objective was to assess the incidence of warfarin-related minor bleeding events.

### 2.4.3. Study design

A prospective interventional quantitative study was conducted to assess warfarin dosing using the Hamberg PK/PD model in two groups of post-operative cardiac surgical children.

Group 1 included patients who had just started warfarin treatment for the first time after cardiac surgery, thus they were considered warfarin naïve patients. In this group, initial

and maintenance warfarin doses were estimated using the model over a 6 month duration and compared to historical case-matched controls dosed according to the traditional 'trial and error' approach. The historical control design was adopted in this group as there is only a limited number of children presenting for cardiac surgery who are eligible for post-operative oral anticoagulation with warfarin. These include children presented for Fontan procedure or replacement of the mitral or aortic valves and their number can be as low as one patient presented for surgery per month. Therefore, such type of study design would reduce the time required to accomplish recruitment of participants (Friedman, Furberg and DeMets, 1998).

Group 2 patients (Figure 8) included children who were established on maintenance warfarin therapy. These patients entered a randomised crossover study comparing model-estimated dose adjustments with the traditional approach, over a 12-month period. No washout period was included in this study as these patients should be maintained on the recommended level of anticoagulation. Warfarin treatment could not be stopped unless it was otherwise recommended by the doctors prior to undergoing certain procedures like cardiac catheterisation or dental procedures where warfarin treatment should be stopped a few days before the procedure and resumed immediately after it. The crossover study design was considered to be advantageous for the present study because of several reasons. First, each patient serves as his/her own control which allows a within-patient comparison of treatment interventions, thus it helps to reduce inter-individual variability in response. In addition, a smaller sample size, in comparison with parallel design, can be used to detect statistically significant differences in treatment response and also gives the best unbiased estimations of the differences between treatments (Friedman, Furberg and DeMets, 1998; Chow and Liu, 2014).

This study was a reality research project conducted at the EMCHC where patients were maintained on different dosage forms of warfarin including different generic warfarin tablets and warfarin suspension. Warfarin has almost complete bioavailability after oral, rectal and intravenous administration (Hogg and Weitz, 2018). In addition, bioequivalence should be demonstrated for the different generics and formulations of a medicinal product before they are approved for patients' use (Morais and Lobato, 2010).

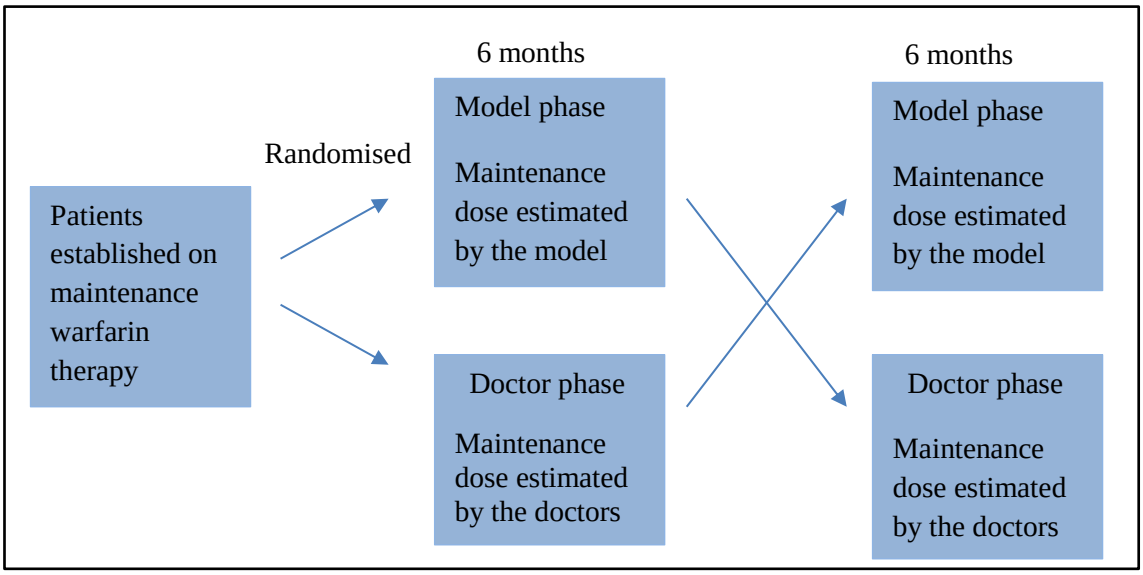


**Figure 8. Design of the randomised, open label, two-period, cross-over study of Group 2 patients.** Patients were randomised to either the Model phase or the Doctor phase and followed up for 6 months in each phase. They were then crossed-over to the alternative phase and followed up for further 6 months.

### 2.4.4. Study participants

Eligible participants for the study were children from birth to 18 years who are under the care of the EMCHC at Glenfield Hospital, Leicester. Eligible participants for Group 1 were identified pre-operatively during the pre-operative clinic visits or from the weekly surgical lists of patients to be admitted for cardiac surgery. However, there was one occasion where the decision to replace the heart valve was made intra-operatively.

Therefore, the patient was identified post-operatively in the intensive care unit. The control patients were identified from the EMCHC database based on age, indication for warfarin therapy and target INR range. For Group 2, eligible participants were identified from the EMCHC database. They were first approached by one of the cardiac liaison nursing team either during the regular phone calls to report the scheduled INR measurements or during the scheduled follow up hospital visits.

#### 2.4.4.1. Inclusion criteria

The inclusion criteria included children from birth to 18 years with congenital heart disease who had been treated or would be treated with warfarin after undergoing reconstructive heart surgery.

#### 2.4.4.2. Exclusion criteria

The exclusion criteria included patients aged over 18 years who were treated as adults, children who refused assent and parents who refused consent and any significant disease which, in the opinion of the direct care team, might either put the participant at risk because of study participation or adversely affect the participants' ability to participate in the study.

### 2.4.5. Study outcomes

The outcome measure of the study was to assess the difference between the model-based and traditional warfarin dosing approaches in:

Group 1:

1. Time taken to achieve first therapeutic INR.
2. Time taken to achieve stable anticoagulation.
3. Time taken to over-anticoagulation.

Group 1 and Group 2:

1. The percentage of INR measurements within the target therapeutic range (%ITR).
2. Percentage of time in target therapeutic range (%TTR).
3. Frequency of INR measurements expressed as the number of INR measurements per month per patient.
4. Frequency of dose alterations.
5. Number of INR values ≥4.0 and ≥ 5.0.
6. The incidence of warfarin-related minor bleeding events.

Stable anticoagulation was defined as at least three consecutive INR measurements in the target therapeutic range (TTR) over a minimum period of four weeks with no change in warfarin dose (Hamberg et al., 2013). The percentage of time in therapeutic range (%TTR) was determined by linear interpolation (Rosendaal et al., 1993).

### 2.4.6. Rationale for the chosen study outcomes

Several outcomes have been used as measures to assess the quality of oral anticoagulation. The most commonly used surrogate of the safety and efficacy of warfarin therapy is time in therapeutic range. In children, this has been reported either as the percentage of INR values within the therapeutic range (%ITR) (Streif et al., 1999) or alternatively as percentage of time in therapeutic range (%TTR) estimated by linear interpolation approach (Rosendaal et al., 1993; Bauman et al., 2010). The former measure, %ITR, is easy to calculate; however, it underestimates the time in therapeutic range, particularly in the periods of instability during which the INR is tested more frequently for dose adjustment. On the other hand, the linear interpolation approach allocates an INR value for each day between subsequent INR tests and thus is more likely to decrease the impact of multiple out-of-range INR values during unstable periods. At

the same time, it gives more importance to the longer stable periods of less INR tests. Nevertheless, this approach also has its own limitations. It involves more complex calculations to estimate time in therapeutic range, it assumes a linear change of INR between each time point which may not be true and it can be biased by INR values that are far outside the target range (BISS et al., 2011). Therefore, both approaches were used to estimate time in therapeutic range in the current study.

Other outcome measures that are commonly used to assess anticoagulation control include dosing requirements, time to first therapeutic INR, number of INR tests (per patient per month), number of dose changes (per patient per month), INR values above the target therapeutic range and the incidence of warfarin-related adverse events (Streif et al., 1999; BISS et al., 2013). These outcomes were also included in the present study.

### 2.4.7. Regulatory and ethical considerations

#### 2.4.7.1. Ethical approvals

Conducting any research that involves human subjects requires that the study protocol be reviewed and approved by an independent research ethics committee. Therefore, in accordance with De Montfort University's research ethics guidelines, the study protocol was submitted to the Ethics Committee of the Faculty of Health and Life Sciences at De Montfort University and approval was granted in 25/03/2015 (Reference number 1527). As the research involved patients under the NHS care, the regional ethics committee approval and the University Hospitals of Leicester (UHL) approval were also required. Hence, the study protocol was submitted to East Midlands – Nottingham 1 Research Ethics Committee and approval was obtained in 16/09/2015 (Reference number 15/EM/0325). The ethical approval of the Research and Innovation Office at the UHL

was subsequently obtained in 14/10/2015 (Reference number UHL 11438) after which the study commenced (Appendix 2).

#### 2.4.7.2. Informed consent

Before children's participation in the study, their parents/legal guardians were asked to give written informed consent to participation. Children over 12 years of age were also asked to provide written informed assent before their participation in the study.

#### 2.4.7.3. Ethical issues

This study involved the evaluation of a new PK/PD based model of warfarin dosing in children. The main ethical issues relating to this study were that children would be subjected to a warfarin dose estimation model that had not been tested in routine clinical practice. Therefore, any unforeseen risks of under- or over-dosing were mitigated by the following measures. First, all model-estimated doses were reviewed and then prescribed by a member of the paediatric cardiology medical team. Second, prescribers were free to override model-estimated doses and select an alternative dose. Third, regular INR monitoring would identify over- or under-anticoagulation.

### 2.4.8. Study procedures

#### 2.4.8.1. The process of warfarin dosing/monitoring at the EMCHC in Glenfield hospital

Warfarin treatment usually starts 2-3 days post-operatively depending on the patient's general condition. During their hospital stay, parents and patients, if old enough, receive information about warfarin including the dosing, monitoring, adverse events and drug and food interactions. After discharge from the hospital warfarin monitoring is performed mostly using home INR monitoring machines apart from some families where the INR

monitoring is performed in the hospital. Families who use the home monitoring machines telephone the cardiac liaison nursing (CLN) team at Glenfield hospital with the INR test result together with information about any intercurrent illness and/or medication use that may affect the anticoagulation stability. The CLN team then transfers this information into the patient's INR charts which are subsequently transferred to the doctors who prescribe the next warfarin dose and INR test schedule. The INR test results for patients who perform their INR tests in the hospital are also transferred into their INR charts and provided to the doctors for warfarin prescription. The CLN team then telephone the families back with the next warfarin dose and INR test schedule. This process is performed by the nurses on the children's ward when families telephone the INR test results or come to the hospital to perform the INR test out of the workday hours.

Therefore, the hospital visits of patients on home INR monitoring is infrequent, usually every 3-6 months. This has affected the consent process of Group 2 patients as will be described in the next section.

During the study, the families reported the INR test results as described earlier. The nurses then telephoned these results to the researcher to adjust warfarin dose and telephone it back to the nurses.

**2.4.8.2. The consent process**

For Group 1 patients, participant information sheets were provided to the parents to consider participation in the study. Written informed consent was obtained either pre-operatively, on the day of admission, or post-operatively prior to commencing warfarin treatment.

For Group 2 patients, because of the infrequent hospital visits of these patients, study packages were posted by the researcher to the families. These packages contained

participant information sheets and blank consent forms for the parents and participant information sheets and blank assent forms for patients older than 12 years. Subsequent phone calls were arranged by the researcher to discuss the study with the families who were asked to sign the consent/assent forms, if they were interested to participate, and post them back to the research team.

Consent and assent forms for Group 1 and Group 2 participants are demonstrated in Appendix 3.

#### 2.4.8.3. Randomisation of Group 2 patients

The randomisation of Group 2 patients was performed using the envelopes method. Fifteen paper slips were labelled (A→B) for patients to be randomised to the Doctor phase and 15 others were labelled as (B→A) for those to be randomised to the Model phase. An independent person was asked to randomly allocate the paper slips into 30 consecutively numbered envelopes and seal them. The envelopes were then consecutively allocated to patients enrolled in the study.

#### 2.4.8.4. Mouth swab and genetic test

Mouth swabs for genotyping of CYP2C9 and VKORC1 were obtained from Group 1 patients either pre-operatively or post-operatively prior to the initiation of warfarin treatment. For Group 2 patients, mouth swabs were obtained on the day of their hospital visits. Genetic testing was performed using a point of care genotype testing instrument, the ParaDNA® (from LGC). This instrument is a rapid Polymerase Chain Reaction (PCR) thermal cycler that uses the HyBecon® probes (Howard et al., 2011) to genotype CYP2C9*2, CYP2C9*3 and VKORC1 -1639G>A in less than one hour. The samples were obtained from the patients and were then transferred to ParaDNA® instrument for target DNA sequence amplification by PCR and detection by melting curve analysis

(Figure 9). The ParaDNA® analysis software (version 2.0) reports CYP2C9*2, CYP2C9*3 and VKORC1 genotypes based on duplicated test results. The software also enables the user to view the melting curve data to determine how a particular genotype call (result) was made (Figure 10).

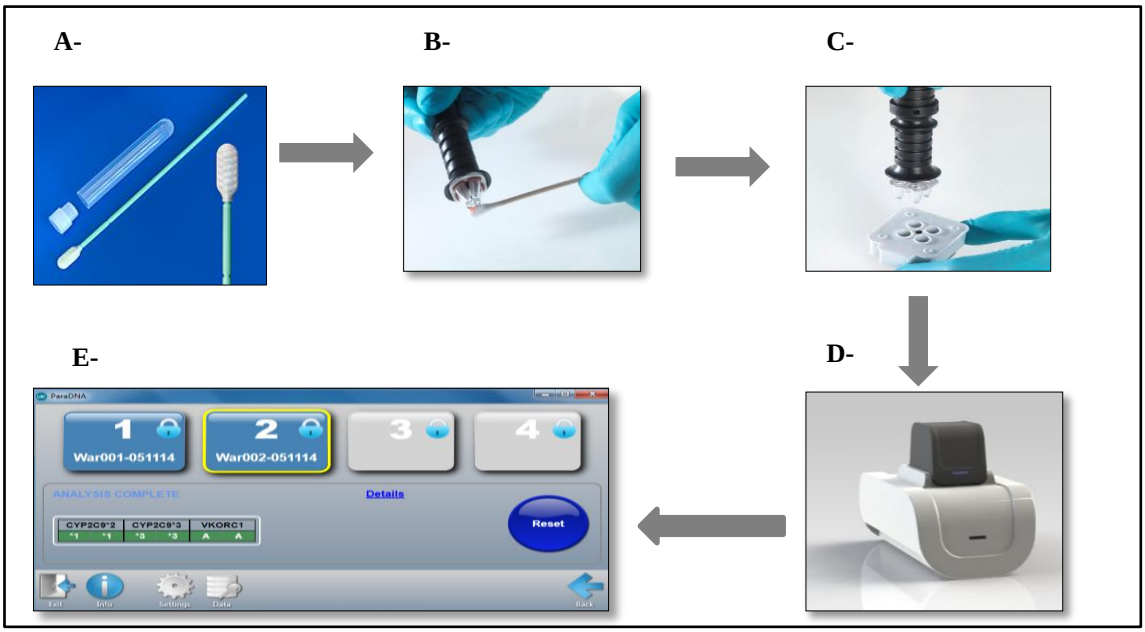


**Figure 9†.** Example of the genotyping process of CYP2C9*2 and *3 and VKORC1. (A) The buccal sample is obtained by swabbing the inside of each cheek for 15 seconds. (B) The buccal swab is sub-sampled into the ParaDNA® Sample Collector (C) The Sample Collector is inserted into the ParaDNA® reaction plate (D) The reaction plate is inserted into the ParaDNA® instrument for the PCR which takes 45 minutes to complete (E) The sample genotype result is shown after the reaction is complete.
†Picture A was obtained from Isohelix® website available at http://www.isohelix.com/products/isohelix-dna-buccal-swabs/. Pictures B through E were obtained from the LGC ParaDNA® User Guide after permission.

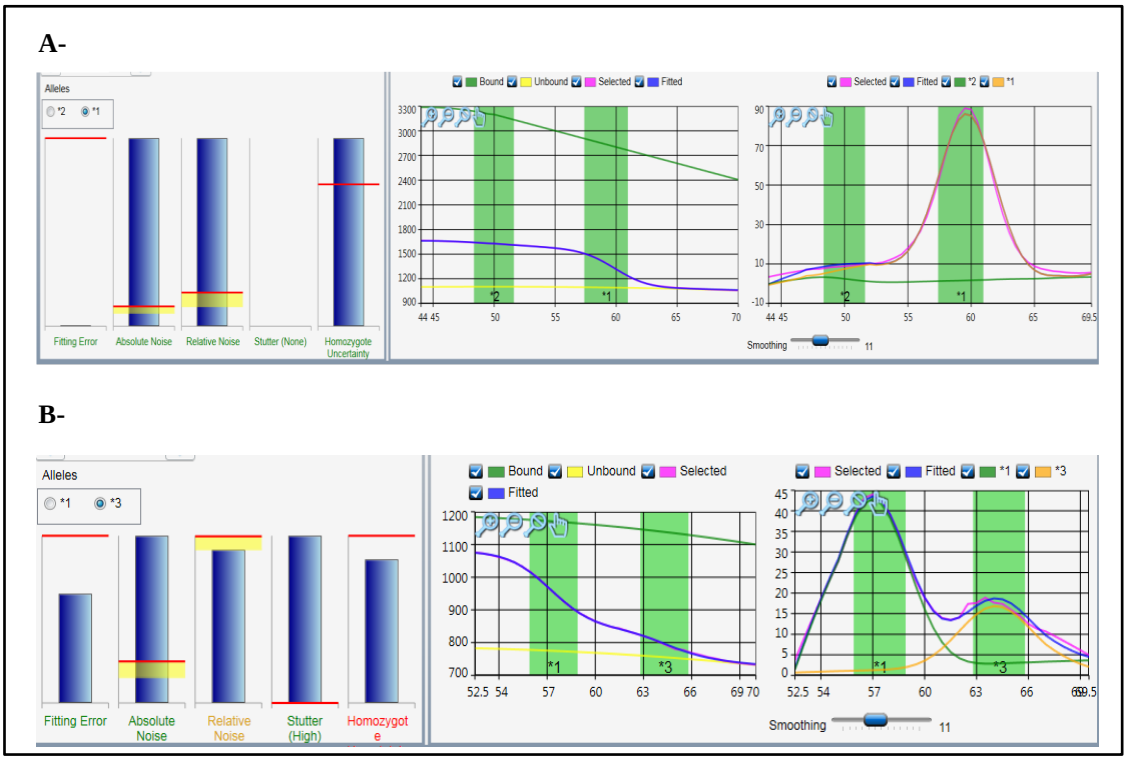


**Figure 10†.** Example of melting curve data. A- A homozygote *1/*1 confident call. B- A call with uncertainty
The bar charts on the left represent the tests that should be passed for the call to be confident. The red lines represent a threshold value and the yellow bands represent areas of uncertainty.
† Picture A was obtained from the LGC ParaDNA® User Guide after permission. Picture B is the genotype call of one of the study participants.

### 2.4.8.5.Warfarin dose estimation

After obtaining the genotyping results of Group 1 patients, initial warfarin doses were estimated using the warfarin dosing model as described earlier in section 2.2. The model predicted doses were then rounded to practical doses for convenient administration to the patient according to the dosage forms available (0.5 mg, 1.0 mg, 3.0 mg and 5.0 mg tablets and 5.0 mg/5.0ml suspension) (Appendix 4). The practical doses were then reviewed and prescribed by the doctors before administration to the patients. Excel files were created for each individual patient and they were updated after every INR feedback for the estimation of individual patient's parameters and subsequent prediction of the tailored maintenance (*a posteriori*) dose (section 2.2). The individual fits of the predicted

INR curves (Figure 5) were assessed. It was sometimes necessary to exclude some INR observations, particularly those that are far above or below the target range, to get the best fit curve for more accurate dose adjustment.

For Group 2 patients who were allocated to the Model phase, Excel files were created for each patient using the last two-months history of warfarin dosing/INR monitoring. This data was used for the prediction of individual patients' parameter estimates and subsequently, maintenance doses (section 2.2). In case of stable patients where the INR tests were infrequent, for example once every 3 to 4 weeks, at least 3 to 5 INR test results were initially used. The Excel files were updated after every INR feedback was obtained from the patients for the estimation of individual patient's parameters and subsequent dose adjustments. The model estimated doses were also rounded to practical doses (Appendix 4) which were then reviewed and prescribed by the doctors. Genetic testing was not required in this group to estimate warfarin maintenance doses as the model is capable of predicting the phenotype based on the previous warfarin doses and INR values of the patient. However, the genotyping results were used in the final analysis to gain a better understanding of warfarin doses and INR responses in this population.

Warfarin dosing for the control subjects of Group 1 patients and during the Doctor phase for Group 2 patients were prescribed by the doctors according to the usual clinical practice at the EMCHC in Glenfield hospital (Appendix 1).

**2.4.8.6. Symptom diary cards**

Symptom diary cards were provided to parents of Group 1 patients during their hospital stay. The symptom diary cards were posted to parents of Group 2 patients after the signed consent/assent forms were received. The parents were asked to record any minor bleeding events which included bruising, nose bleeds, bleeding gums or the

presence of blood in vomit, cough, urine and faeces. The parents were also asked to record the start/end date and time of the bleeding episodes. In addition, they were asked to record the action taken to deal with these events whether there was no action required, telephone advice was sought, GP was contacted, or hospital appointment/admission was required. At the end of their enrolment in the study, the parents were asked to send the symptom diary cards back to the research team.

#### 2.4.8.7. Study duration

The follow up period for Group 1 patients was 6 months. The study outcomes were then compared to historical case matched controls. Cases were matched according to age (± 1.0 year), indication and target INR range.

For Group 2 patients, the follow up period was 6 months in each phase of treatment, i.e. a total period of 12 months. The study outcomes were then compared between the two phases of treatment.

### 2.4.9. Statistical analysis

#### 2.4.9.1. Sample size estimate

The sample size for the Group 1 was based on clinical practicalities, depending on the number of patients admitted for surgery, and study feasibility within a reasonable time frame. Hence, for Group1, approximately 10 subjects were estimated to be recruited over a 12-month period.

Sample size for Group 2 was estimated using the method described by Julious *et al* for paired continuous data (Julious, Campbell and Altman, 1999). The primary outcome measure, proportion of observed INR measurements within the therapeutic range, has been utilised. The mean (standard deviation SD) of the proportion of INR measurements within the therapeutic range for the existing database of children at Glenfield hospital was

determined to be 54.06% (16.85). Based on a clinically relevant effect size (difference between model-based and traditional method) of 11% (to increase the proportion of within-range INR measurements to 65%), a standardised effect size (computed using the SD estimate from the existing database) was derived. Hence for 80% power and two-sided 5% significance level, a sample size of 25 was estimated. To allow for some patients dropping out, a total of 30 patients were to be recruited.

**2.4.9.2. Data analysis**

Data analysis was performed using Excel (Microsoft Corp., 2010) and SPSS (IBM Corp., 2013). For Group 1 patients, the characteristics of the study population and the study outcomes were summarised using descriptive statistics as the sample size was very small. For Group 2 patients, the characteristics of the study population were summarised using descriptive statistics. The continuous variables were described as mean (SD) and range for normally distributed data or median and range for data that was not normally distributed. The categorical variables were described as numbers and percentages.

Comparison of the study outcomes between the Model phase and the Doctor phase was performed using paired sample t-test or Wilcoxon test as appropriate. Sensitivity analysis was performed to compare the %ITR and %TTR between the two treatment phases by taking into account the effect of covariates. The covariates included age, weight, indication, target INR range, CYP2C9 genotype, VKORC1 genotype and dosage form used. Therefore, patients were sub-grouped based on these covariates and comparisons were performed accordingly. A Forest plot was used to depict the results of the sensitivity analysis of %TTR for the age, indication and VKORC1 genotype sub-groups and %ITR for CYP2C9 genotype sub-group (because %TTR data for CYP2C9 genotype sub-group was not normally distributed). In addition, sensitivity analysis was performed to compare

the number of dose changes and over-anticoagulation (INR ≥ 4.0 and INR ≥ 5.0) between the two treatment phases by taking into account the effect of indication and target INR range. The patients were sub-grouped based on these covariates and comparison was performed accordingly. The sensitivity analyses were performed using paired sample t-test or Wilcoxon test as appropriate.

The effect of genetic and non-genetic variables on warfarin daily dose requirement and time in therapeutic range, measured as %ITR and %TTR, was also evaluated. The variables included age groups, gender, ethnicity, indication of warfarin, target INR range, CYP2C9 genotype and VKORC1 genotype. The evaluation was performed using independent sample t-test, Mann-Whitney test, analysis of variance (ANOVA) or Kruskal-Wallis test as appropriate.

A p-value of less than 0.05 was considered to be significant.

## 2.5. The qualitative study: Exploration of the experience of patients/parents and health care professionals of warfarin treatment and the new dosing approach

### 2.5.1. Aim of the qualitative study

The aim of the qualitative study was to explore the experience of children, parents and health care professionals about managing warfarin therapy as well as their views of the new warfarin dosing method.

### 2.5.2. Objectives of the qualitative study

The objective of the qualitative study was to explore the lived experience of patients, parents and health care professionals with respect to dosing and monitoring of warfarin therapy. The second study objective was to assess the perceived acceptability of using the model-based warfarin dosing by patients, parents and health care professionals.

### 2.5.3. Study design

Qualitative research approaches have been widely used in health research to gain an in-depth understanding of health, health behaviour and health services. Obtaining a thorough understanding of the human behaviour and the causes, attitudes and incentives of that behaviour can help to enhance health and health services (Green and Thorogood, 2014). The interpretative phenomenological approach was adopted as it involves studying the human experience and how people make sense of their life world (Langdridge, 2007). Interpretative Phenomenological Analysis (IPA) is an idiographic approach that is concerned with the in-depth examination of lived experience and usually involves studying small homogenous samples of individuals who share a particular experience (Smith, Flowers and Larkin, 2009). This would enable the lived experience of being involved in warfarin dosing and monitoring to be described and understood from the perspective of key stakeholders; patients, parents and health care professionals. Stakeholders' perceived value of the new warfarin dosing method was also appraised.

### 2.5.4. Study participants

Eligible participants for the qualitative study were patients older than 12 years and/or parents of children on long-term warfarin treatment. Also, doctors and nurses who were involved in the process of warfarin dosing/monitoring at the EMCHC at Glenfield hospital were eligible.

The inclusion criteria were children older than 12 years who had been treated with warfarin and/or their parents in addition to doctors and nurses who were involved in warfarin dosing/monitoring.

### 2.5.5. Outcome measures

The qualitative study aimed at exploring two outcomes. First, the experience of medical and nursing staff when managing warfarin therapy in children and their perceptions of the value of the model-based warfarin dosing. Second, patients' and/or parents' lived experience of managing warfarin therapy and their experience of using the model-based warfarin dosing.

#### 2.5.5.1. Rationale for the study outcomes

In order to ensure the safe and effective use of warfarin and enhance adherence to its therapy, it is pivotal to obtain an insight into the experience of both the health care professionals and patients/carers with warfarin treatment. Exploring the experiences of doctors, nurses, patients/carers with warfarin prescribing and monitoring has been used in adult patients to get an in-depth understanding of the attitudes about warfarin therapy, the barriers encountered in the process of warfarin prescribing and monitoring, the individual role in this process and the best strategies to improve warfarin use (Bajorek et al., 2006; Bajorek et al., 2007; Stafford et al., 2012). Thus, it is essential to explore the experience of the key stakeholders of warfarin therapy in children where the treatment is intensely challenging.

### 2.5.6. Study procedures

#### 2.5.6.1. Informed consent

The written informed consent/assent of patients/parents for the qualitative study was obtained as part of their consent/assent for participation in the prospective clinical study. Health care professionals were also asked to provide written informed consent prior to

their participation in the qualitative study. The consent form of health care professionals is demonstrated in Appendix 3.

#### 2.5.6.2. Data collection

To achieve the objectives of the study, in-depth semi-structured interviews were chosen as the data collection approach with representatives from all the key stakeholders. Interviews were chosen because they enable the exploration of the participants' perceptions, feelings, beliefs, attitudes and experiences with the topic under investigation (Holloway and Wheeler, 2010). Semi-structured interviews are widely used in qualitative research (Holloway and Wheeler, 2010). The interview questions are relatively few and specific, focusing on the principal areas required to be explored. The researcher, however, can further explore these areas by prompting the participants for more elaboration to obtain a better understanding of the issues under investigation. The order of questions is not the same for every interview and depends on the responses of participants. The interview questions (and prompts) are contained in an interview guide which helps the researcher to collect similar data from all participants (Holloway and Wheeler, 2010).

#### 2.5.6.3. Sampling and sample size

The sampling method adopted in recruiting participants was purposive. This is the most commonly used method of sampling in qualitative research that involves selecting participants that are more likely to generate detailed rich data depending on the topic under research and the practicalities of the research (Green and Thorogood, 2014). IPA aims at selecting participants on the basis that they can provide a particular perspective of the investigated phenomena (Smith, Flowers and Larkin, 2009). The perspectives of parents of children, teenager patients receiving warfarin treatment and healthcare professionals were sought in this study. Therefore, for Group 1 and Group 2 participants,

interviewees were recruited from those study participants who come to Glenfield Hospital either for routine medical visits or for hospital INR monitoring for more convenience to the researcher and participants. The sample included parents of young children as well as a parent and a teenager patient to get an insight of the experience of managing warfarin treatment from the perspective of parents as well as the teenage patient. For the health care professionals, interviewees included doctors who are involved in warfarin dosing/monitoring as well as cardiac liaison nurses who are involved in warfarin monitoring.

IPA is usually based on small samples as the issue is the quality of data, not quantity, and hence, sample sizes of 3 to 6 participants has been suggested (Smith, Flowers and Larkin, 2009). Therefore, interviews were planned to be conducted with 4 families (2 from Group 1 and 2 from Group 2) and 5 healthcare professionals (1 paediatric cardiology consultant, 2 paediatric cardiology registrars and 2 paediatric cardiac liaison nurses).

**2.5.6.4. Interviewing of patients/parents and health care professionals**

Topic guides were developed for Group 1 participants, Group 2 participants and health care professionals (Appendix 5). Potential interviewees from Group 1 and Group 2 families were approached either during their hospital visits or through phone calls to ask them if they were willing to be interviewed. If participants were interested to be interviewed, an interview appointment was made at a convenient time in Glenfield Hospital. Potential participants from the health care professionals were approached at their usual work place and were asked if they were willing to be interviewed. Interviews were conducted with the health care professionals who agreed to participate in the study at a convenient time in Glenfield Hospital.

For Group 1 participants, the interviews were conducted around the end of the 6-month period of model-based warfarin treatment. In contrast, two interviews were conducted for each Group 2 participant; the first interview was conducted around the end of the 6-month period of doctors' dosing and prior to cross-over to the model-based dosing phase, whereas the second interview was conducted around the end of the 6-month model-based treatment phase. Interviews with health care professionals were conducted about 6 months after the study has started. This period was roughly chosen to allow the health care professionals to have adequate experience with model-based warfarin dosing/monitoring before exploring their views of the new dosing approach. The interviews were all face-to-face except for the second interview of a Group 2 patient and his mother where it was not convenient for them to come to Glenfield Hospital, therefore a telephone interview was arranged. The interviews were audio-recorded and then transcribed verbatim and analysed manually by the researcher. Thematic analysis, using a phenomenological approach, was used to code important words/statements in the transcripts into themes to help understand the experience of patients/parents and health care professionals of managing warfarin therapy (Appendix 6).

# Chapter Three

## Validation of the Hamberg PK/PD model

# Chapter 3: Validation of the Hamberg PK/PD model

## 3.1. Introduction

Oral anticoagulation with warfarin represents a major challenge to successful drug therapy in children due to various factors. Demographic, genetic, clinical and environmental factors have been shown to contribute to the wide inter-individual variability in the drug's dose requirements and treatment outcome (Biss et al., 2012; Hamberg et al., 2014).

For this reason, various attempts have been made to develop models that account for the factors that contribute to this variability in an attempt to individualise warfarin dose in children and hence improve the treatment outcome. These models were either linear regression models (See Chapter 1 Table 4) or PK/PD models (Hamberg et al., 2013; Lala et al., 2013). The predictive performance of these models has been evaluated by comparing the model-predicted doses with the actual prescribed doses. The Hamberg model (Hamberg et al., 2013) was shown to be superior to other models in predicting ideal doses, i.e. those that are within 20% of the actual doses prescribed to children (Hamberg and Wadelius, 2014; Marek et al., 2016).

This study was undertaken as a first step, and prior to the prospective clinical study, to assess the predictive performance of the Hamberg model in a cohort of post-operative cardiac children on long-term warfarin treatment at the EMCHC.

## 3.2. Methodology

See Chapter 2, Section 2.3.

### 3.3. Results

#### 3.3.1. Patient characteristics

Data from 87 warfarin-treated patients who were present on the EMCHC database was collected during July and August 2014. Twenty-seven patients were excluded from the analysis due to missing treatment and monitoring histories. Sixty patients with data from the initiation of warfarin treatment as well as a stable treatment period were used for the evaluation of the model. The characteristics of the study subjects are summarised in Table 5.

**Table 5. Characteristics of paediatric patients included in the evaluation of the Hamberg model.**

| | |
|---|---|
| Age* (years), median (range) | 5.2 (1-15.9) |
| Weight* (kg), median (range) | 16.75 (8.4-66.6) |
| Gender, N (%) | |
| Male | 39 (65) |
| Female | 21 (35) |
| Ethnicity, N (%) | |
| White | 43 (71.7) |
| Asian | 8 (13.3) |
| Other‡ | 8 (13.3) |
| Missed | 1 (1.7) |
| Indication for warfarin, N (%) | |
| Fontan | 41 (68.3) |
| AVR | 10 (16.7) |
| MVR | 6 (10) |
| Other† | 3 (5) |
| Target INR range, N (%) | |
| 2.0-3.0 | 23 (38.3) |
| 1.5-2.5 | 16 (26.7) |
| 2.5-3.5 | 8 (13.3) |
| 2.0-2.5 | 7 (11.7) |
| Other§ | 6 (10) |
| *At the time of first dose/INR observation.<br>‡ Other ethnicity include Black, mixed White and Asian, mixed White and Black Caribbean and Middle Eastern.<br>† Other indications include Kawasaki disease and stroke.<br>§ Other target INR ranges include 1.5-3.0, 1.5-3.5, 2.0-3.5, 2.5-3.0 and 3.0-3.5.<br>AVR is aortic valve replacement.<br>MVR is mitral valve replacement. | |

The median age was 5.2 years and the median weight was 16.75 kg. Most of the study subjects were male (65%) and most of the patients were of white ethnicity (71.7%). The most common indication for warfarin anticoagulation was Fontan procedure (68.3%) and the most common target INR range was 2.0-3.0 (38.3%).

### 3.3.2. Study outcomes

Results of the validation of the Hamberg model are presented in Table 6. Seventy percent of the dose predictions were ideal, i.e. within ± 20% of the observed doses whereas 25% of the predicted doses were underestimated and 5% were overestimated (Figures 11 and 12). The bias was -0.10 which implies an overall dose underprediction of 0.1 mg. The precision was 0.19 which gives an idea of the proximity of dose predictions to each others (Figure 11). This implies an imprecision of 19%.

**Table 6. Results of the validation of the Hamberg model on a cohort of 60 children after congenital heart surgery at the EMCHC.**

| Ideal doses (%) | Overestimated doses (%) | Underestimated doses (%) | Bias | Precision |
|---|---|---|---|---|
| 70 | 5 | 25 | -0.10 | 0.19 |

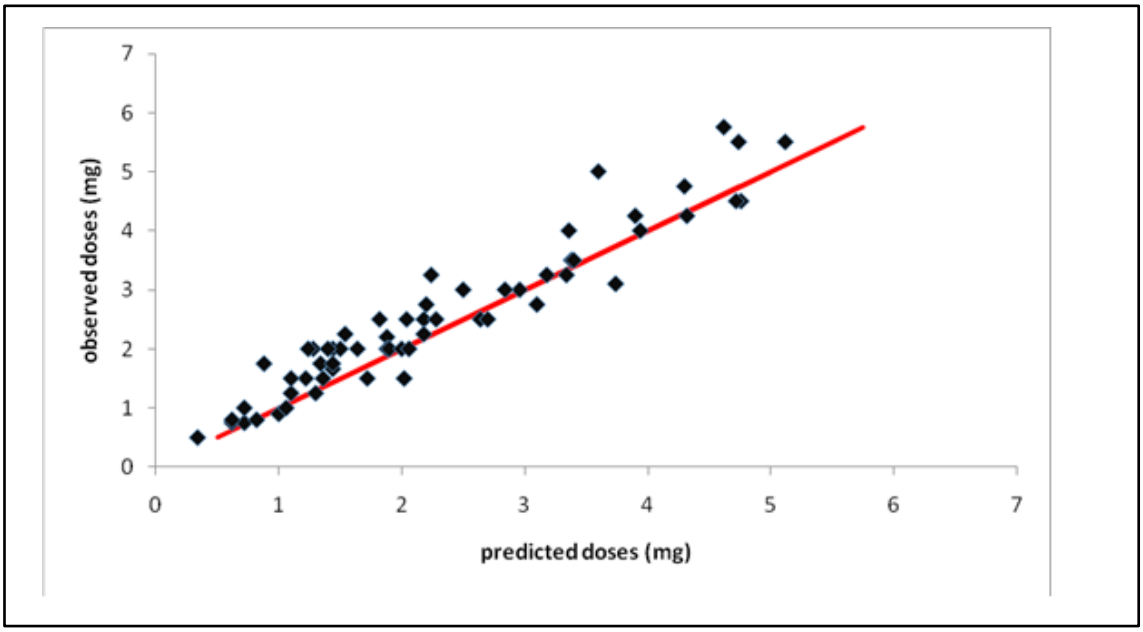


**Figure 11.** Observed vs model-predicted warfarin maintenance doses for the study cohort.

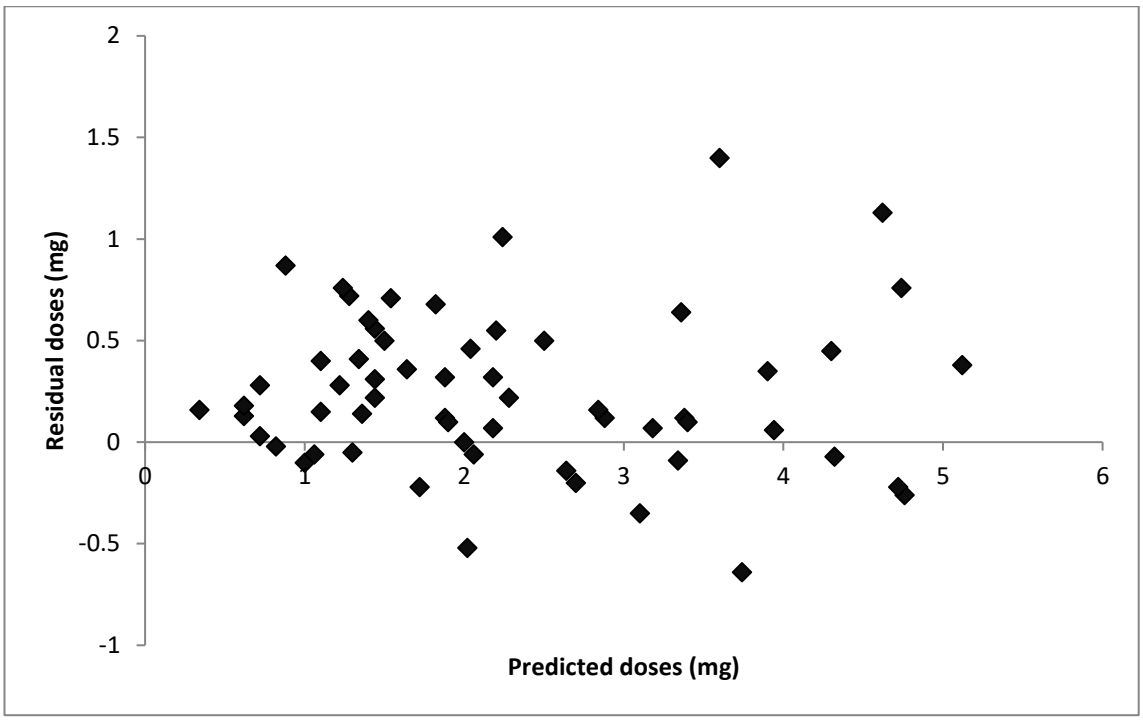


**Figure 12.** Model-predicted doses were plotted against residual doses calculated as (observed dose-predicted dose). Data points with positive values on the Y axis indicate dose underprediction while those with negative values indicate dose overprediction.

Age was found to be significantly positively correlated with the observed dose ($p= 0.001$, $r= 0.43$). However, there was a non-significant negative correlation of age with the weight-adjusted dose ($p= 0.29$, $r= -0.14$) (Figure 13). Younger patients aged 1-5 years required significantly lower maintenance doses than the older ones i.e. those aged 6-10 and 11-18 years (Figure 14 and Table 7). In contrast, the weight-adjusted daily dose did not vary significantly among the three age groups ($p= 0.34$) (Table 7). Weight was also found to correlate significantly with the observed dose ($p<0.05$, $r= 0.49$).

Patients anticoagulated after Fontan procedure required significantly lower daily maintenance doses than all other indications of warfarin use ($p= 0.005$) (Figure 15 and Table 7). In contrast, the weight-adjusted daily dose did not vary significantly among the four indication groups of warfarin treatment ($p= 0.12$) (Table 7). The daily warfarin

maintenance dose varied significantly among the target INR ranges (p= 0.015) (Figure 16 and Table 7). However, the weight-adjusted dose did not vary significantly among the target INR ranges (p= 0.23) (Table 7). Ethnicity was not found to significantly influence the daily dose (p= 0.73) and the weight-adjusted dose (p= 0.82). In addition, gender did not significantly affect the daily dose (p= 0.27) and the weight-adjusted dose (p= 0.31) (Table 7).

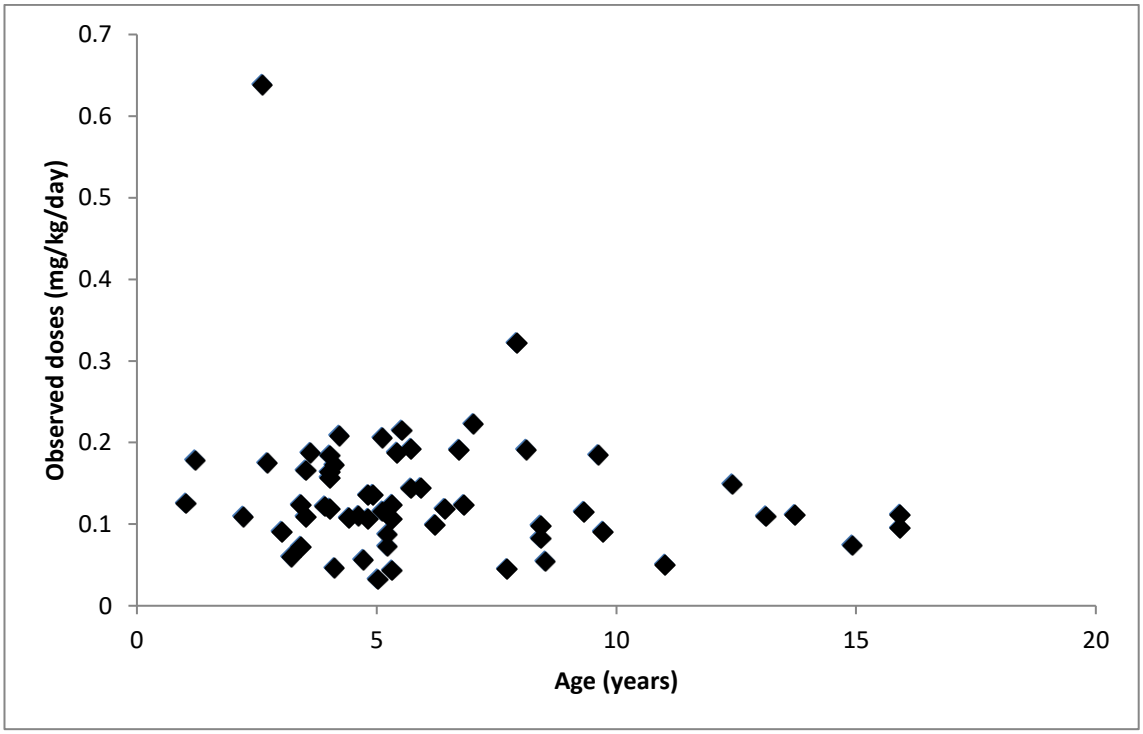


**Figure 13.** Relationship between observed warfarin maintenance doses (mg/kg/day) and age.

**Table 7. Descriptive statistics and p-values of the effect of demographic and clinical variables on warfarin dose.**

| | | Warfarin dose (mg/day) | | | | Warfarin dose (mg/kg/day) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **N** | **Median** | **Minimum** | **Maximum** | **p-value** | **Median** | **Minimum** | **Maximum** | **p-value** |
| **Age groups (years)** | | | | | | | | | |
| **1-5** | 39 | 2.0 | 0.5 | 5.75 | 0.002† | 0.13 | 0.03 | 0.64 | 0.34† |
| **6-10** | 14 | 2.9 | 0.75 | 5.5 | | 0.12 | 0.05 | 0.32 | |
| **11-18** | 7 | 4.5 | 1.75 | 5.5 | | 0.11 | 0.05 | 0.15 | |
| **Gender** | | | | | | | | | |
| **Male** | 39 | 2.5 | 0.75 | 5.75 | 0.27§ | 0.12 | 0.04 | 0.64 | 0.31§ |
| **Female** | 21 | 2.0 | 0.5 | 5.5 | | 0.11 | 0.03 | 0.32 | |
| **Ethnicity** | | | | | | | | | |
| **White** | 43 | 2.2 | 0.5 | 5.5 | 0.73† | 0.12 | 0.03 | 0.32 | 0.82† |
| **Asian** | 8 | 2.13 | 0.75 | 4.0 | | 0.13 | 0.05 | 0.21 | |
| **Other** | 8 | 2.25 | 1.0 | 3.5 | | 0.13 | 0.06 | 0.19 | |
| **Indication** | | | | | | | | | |
| **Fontan** | 41 | 2.0 | 0.5 | 4.25 | 0.005† | 0.12 | 0.03 | 0.22 | 0.12† |
| **AVR** | 10 | 3.88 | 2.0 | 5.5 | | 0.11 | 0.05 | 0.22 | |
| **MVR** | 6 | 3.63 | 0.75 | 5.75 | | 0.2 | 0.05 | 0.64 | |
| **Other** | 3 | 2.5 | 1.25 | 4.5 | | 0.13 | 0.1 | 0.18 | |
| **Target INR range** | | | | | | | | | |
| **1.5-2.5** | 16 | 2.0 | 0.5 | 2.5 | 0.02† | 0.11 | 0.03 | 0.18 | 0.23† |
| **2.0-3.0** | 23 | 2.25 | 0.8 | 5.0 | | 0.12 | 0.05 | 0.22 | |
| **2.5-3.5** | 8 | 4.13 | 0.75 | 5.75 | | 0.19 | 0.05 | 0.64 | |
| **2.0-2.5** | 7 | 2.75 | 0.75 | 3.5 | | 0.17 | 0.05 | 0.32 | |
| **Other** | 6 | 1.75 | 1.25 | 4.75 | | 0.12 | 0.03 | 0.64 | |

§ Mann-Whitney U test.
† Kruskal-Wallis test.

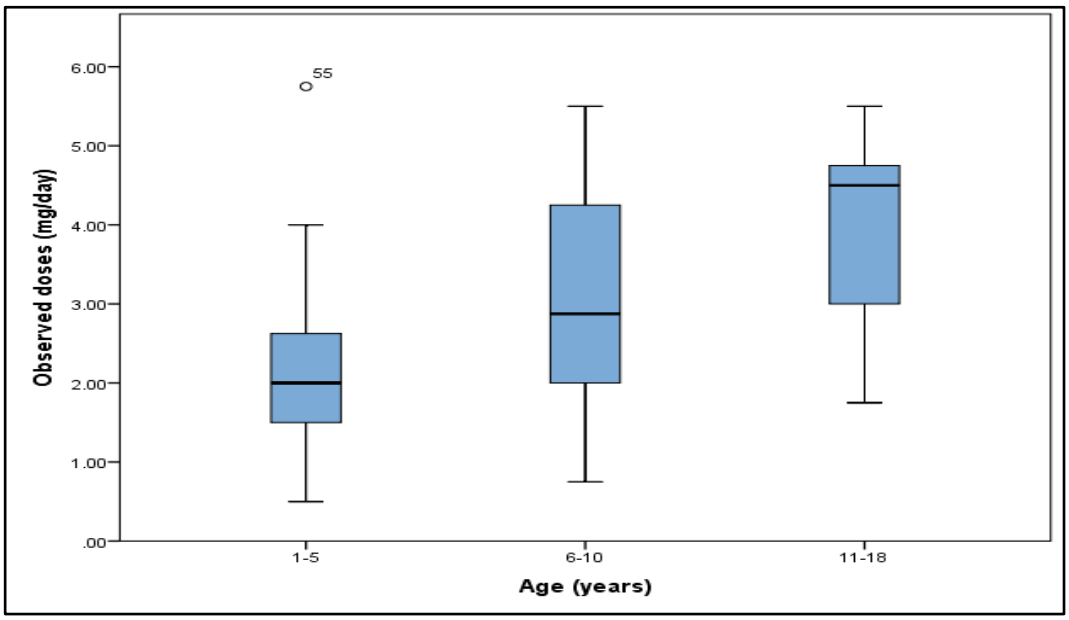


**Figure 14.** Box plot showing the relationship between observed warfarin maintenance doses and age.

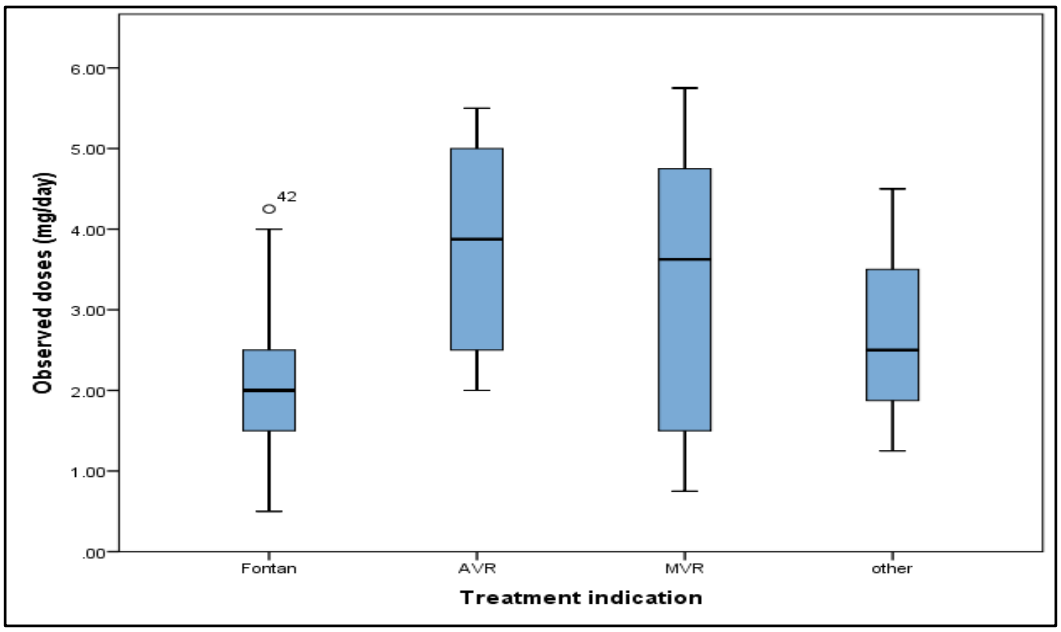


**Figure 15.** Box plot showing the influence of treatment indication on the observed warfarin maintenance doses.

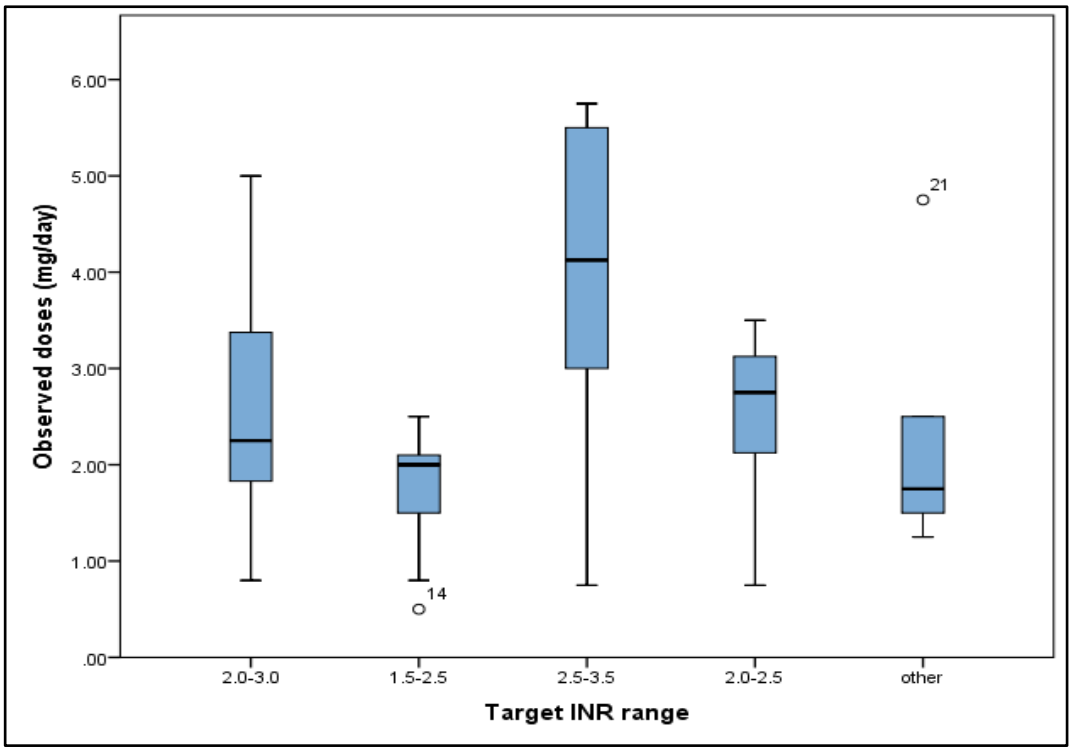


**Figure 16.** Box plot showing the effect of target INR range on the observed warfarin maintenance doses.

### 3.4. Discussion

This study has evaluated the predictive performance of the Hamberg model using retrospectively collected data from a cohort of children on the EMCHC database who were maintained on long-term warfarin treatment. The model performed well in predicting warfarin doses in this cohort (70% ideal dose predictions, bias -0.1 and precision 0.19), however, a tendency towards dose underestimation was observed. The predictive performance of the Hamberg model has also been evaluated in a cohort of 49 children on warfarin treatment (Hamberg et al., 2013). The ideal dose prediction was 70% with bias of -0.04 and precision of 0.57. In this study, the model showed a tendency to underestimate warfarin doses in children younger than 2 years of age. This has been

attributed to the likelihood of PK parameters underestimation due to underestimation of the metabolic capacity by the bridged model in this age group (Hamberg et al., 2013). However, the underestimated doses in the current retrospective evaluation were observed in children aged between approximately 3 and 16 years and hence PK parameters underestimation is unlikely to be an explanation for these findings. Information about CYP2C9 and VKORC1 genotypes was not available for dose predictions in this retrospective analysis. Yet, the model estimates maintenance (*a posteriori*) doses based on the individual parameter estimates which become more refined and patient-specific as more INR observations are obtained (Hamberg et al., 2015). It is also important to know that warfarin dose predictions in the current study were performed in a slightly different way than was performed by Hamberg *et al*. (2013). In the current study, the warfarin dose predictions were based on INR observations from the beginning of warfarin treatment until the first stable warfarin treatment period was achieved. In contrast, only 3 INR observations prior to the stable treatment period were used by Hamburg *et al*. (2013). The reason behind this was the low percentage of ideal predicted doses (48.3%) obtained using only 3 INR observations prior to the stable treatment period. Therefore, longer treatment history was required for better dose prediction. This may be attributed to the software used for dose predictions. Warfarin dose predictions in the current study were performed using the Java-based dose decision tool (Hamberg et al., 2015), whereas NONMEM software was used for dose predictions in Hamberg *et al*. (2013) study. Comparison of the maintenance (*a posteriori*) dose predictions between the Java-based dose decision tool and NONMEM software has shown a mean difference of 5% in dose predictions between the two software (Hamberg et al., 2015).

The effect of demographic and clinical factors on warfarin maintenance dose was also evaluated in this cohort. Age and weight were found to be significantly positively correlated with dose. This is consistent with previous findings obtained in children that have shown statistically significant correlations for age and weight with warfarin dose (Biss et al., 2012; Moreau et al., 2012; Shaw et al., 2014; Wakamiya et al., 2016). In agreement with previous studies in children (Streif et al., 1999; Biss et al., 2012; Shaw et al., 2014), patients with Fontan circulation were found to require significantly lower maintenance doses than other indications of warfarin use. This may be attributed to the lower levels of anticoagulation required for these patients as indicated by the lower target INR ranges used or to an underlying abnormality in liver function (Whiteside et al., 2016; Kaulitz et al., 1997). The target INR range was also shown to significantly affect the warfarin dose requirements. This finding was similar to that obtained in two previous studies in children that have demonstrated the significant effect of the target INR range on warfarin maintenance dose (Moreau et al., 2012; Wakamiya et al., 2016).

The most important advantage of the Hamberg model is its ability to adjust warfarin *a posteriori* (maintenance) doses by taking into account factors other than those included in the model for dose prediction. By estimating the individual model parameters, all factors that can affect warfarin PK and PD can be taken into consideration. For example, the effect of vitamin K intake, drug interactions and underlying medical condition. In addition, the model can handle INR values measured during non-steady state conditions which can help to give information about the rate and extent of response to warfarin treatment in individual patients (Hamberg et al., 2015). However, an important weakness in the model is the tendency toward dose underestimation. Theoretically, this can carry

the risk of under-anticoagulation and subsequent risk of thrombosis, however, it needs to be applied clinically on a prospective basis to evaluate its clinical significance.

The results of clinical accuracy, bias and precision obtained from this retrospective evaluation provided adequate validation for the use of Hamberg model in a prospective clinical study in cardiac children in the EMCHC.

# ***Chapter Four***

## *The prospective clinical study*

## *(Group 1)*

# Chapter 4: The prospective clinical study: Patients starting warfarin for the first time post-cardiac surgery (Group 1)

## 4.1. Introduction

The anticoagulation treatment outcomes during initiation of warfarin therapy in children have been shown to be influenced by genetic and non-genetic factors. (BISS et al., 2013; Hawcutt et al., 2014; Shaw et al., 2014; Ruud et al., 2008). In addition, warfarin dose requirements have been shown to be associated with wide inter-individual variability due to various demographic, genetic and clinical factors (Biss et al., 2012; Hamberg et al., 2014; Moreau et al., 2012; Nguyen et al., 2013; Shaw et al., 2014). Therefore, to individualise warfarin dosing in children and hence improve the treatment outcome, models incorporating variables affecting warfarin dose/response have been developed (Biss et al., 2012; Hamberg et al., 2013; Lala et al., 2013; Vear et al., 2014). However, these models were never tested clinically on a prospective basis. Only one prospective clinical study has been conducted to compare genotype-guided warfarin dosing with the standard dosing in children (Tabib et al., 2015). The genotype-guided dosing was found to significantly decrease the time to stable dose and hospital stay days (Tabib et al., 2015).

This research project involves, for the first time, the prospective clinical evaluation of a mechanistic PK/PD model (Hamberg et al., 2015) in children starting warfarin treatment for the first time after congenital heart surgery.

### 4.2. Methodology

See Chapter 2, Section 2.4.

### 4.3. Results

#### 4.3.1. Patient characteristics

Patient recruitment occurred between October 2015 and December 2016. Nine consecutive patients were screened from whom only 5 consented to participate. The characteristics of Group 1 patients are summarised in Table 8. Five patients were enrolled in Group 1, all were female with age range of 3.8-8.9 years and weight range of 15.4-30.3 kg. Three patients were of Asian ancestry, three patients had Fontan procedure, all the patients were of the wild type CYP2C9 genotype (*1/*1) and three of them were of the wild type VKORC1 genotype (G/G). Only one patient had a concomitant chronic disease which was Type 1 diabetes mellitus. Four of the patients were on the tablet dosage form of warfarin, and in 3 of the cases the tablets were crushed and mixed with water for ease of administration. The comparative characteristics of the control patients are shown in Table 8. The age range of the control subjects was 3.4-9.3 years and the weight range was 16.0-36.5 kg. All the control subjects were of the white ethnicity and 3 of 5 patients were male. The median average daily dose of warfarin was 0.2 mg/kg/day (range 0.1-0.3 mg/kg/day) for the case subjects and 0.1 mg/kg/day (range 0.1-0.2 mg/kg/day) for the control subjects. One patient had Noonan syndrome and hypothyroidism secondary to amiodarone use and one patient had migraine.

**Table 8. Characteristics of the case and control patients.**

| Patient ID | Age[1] (years) | Weight[2] (kg) | Gender | Ethnicity | Indication for warfarin | Target INR range | CYP2C9 genotype | VKORC1 genotype | Average warfarin dose (mg/kg/day) | Baseline INR value | Concomitant chronic diseases | Dosage form used |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 | 5.4 | 18.3 | F | Asian | MVR | 2.5-3.5 | *1/*1 | G/G | 0.3 | 1.8 | Type 1 DM | Tablet[3] |
| Control 1 | 4.2 | 19.1 | M | White | MVR | 2.5-3.5 | NA | NA | 0.2 | 1.1 | None | NA |
| Case 2 | 6 | 16 | F | Asian | Fontan | 2.0-3.0 | *1/*1 | G/G | 0.2 | 1.4 | None | Tablet[3] |
| Control 2 | 5.3 | 16 | F | White | Fontan | 2.0-3.0 | NA | NA | 0.1 | NA* | None | NA |
| Case 3 | 3.8 | 15.4 | F | White | Fontan | 2.0-3.0 | *1/*1 | G/G | 0.2 | 1.1 | None | Liquid |
| Control 3 | 3.4 | 17 | F | White | Fontan | 2.0-3.0 | NA | NA | 0.1 | 1.2 | None | NA |
| Case 4 | 6 | 15.4 | F | White | MVR | 2.5-3.5 | *1/*1 | G/A | 0.2 | 1.5 | None | Tablet[3] |
| Control 4 | 6.7 | 16.9 | M | White | MVR | 2.5-3.5 | NA | NA | 0.1 | 1.0 | Noonan syndrome and hypothyroidism secondary to amiodarone use | NA |
| Case 5 | 8.9 | 30.3 | F | Asian | Fontan | 2.0-3.0 | *1/*1 | G/A | 0.1 | 1.2 | None | Tablet[4] |
| Control 5 | 9.3 | 36.5 | M | White | Fontan | 2.0-3.0 | NA | NA | 0.1 | NA‡ | Migraine | NA |

[1] Age of the case subjects was at enrolment and that of the controls was at the time of first dose/INR observation. [2] Weight of the case subjects was at enrolment and that of the controls was at the time of first dose/INR observation. [3] Tablets are crushed & mixed with water. [4] Tablet swallowed whole but halved to get the 0.5 mg dose. MVR mitral valve replacement. DM diabetes mellitus. NA not available. * INR after a 3.0-mg loading dose was 1.4. ǂ INR after a 3.6-mg loading dose was 1.0.

### 4.3.2. Study outcomes

A total of 436 INR measurements was collected from the case and control subjects over a total follow up period of 5 years. Results of the study outcomes for Group 1 patients and controls are shown individually in Table 9. Descriptive statistics of the results are shown in Table 10.

#### 4.3.2.1. Time to first therapeutic INR, stable anticoagulation and over-anticoagulation

The median time to achieve the first INR values within the target therapeutic range was 5 days for the case subjects compared to 2 days for the control ones (Figure 17). Two of the case patients and one control patient did not achieve stable anticoagulation during the 6-month period of follow up. The median time to stability for the remaining three case patients was 29 days as compared to 96.5 days for the remaining control patients (Figure 18). For the three case patients who achieved stable anticoagulation, two patients attained stability 9 and 15 days faster than their control subjects, respectively. The third patient achieved stability after 29 days of warfarin treatment whereas her control patient did not achieve stability in the 6-month follow up period. The two case patients who did not achieve stability were anticoagulated with warfarin for mechanical mitral valves, their age was 5.4 and 6 years, respectively whereas the control patient who did not achieve it was anticoagulated for Fontan circulation and aged 9.3 years.

The median time to the first INR value ≥4.0 (over-anticoagulation) was 15 days for the case subjects as compared to 4 days for the control group (Figure 17).

**Table 9. Results of the study outcomes for Group 1 case and control subjects.**

| Outcome | Case 1 | Control 1 | Case 2 | Control 2 | Case 3 | Control 3 | Case 4 | Control 4 | Case 5 | Control 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Time to first therapeutic INR (days)** | 6 | 1 | 5 | 2 | 2 | 2 | 5 | 3 | 2 | 3 |
| **Time to stable anticoagulation (days)** | NA‡ | 138 | 87 | 96 | 9 | 24 | NA‡ | 97 | 29 | NA‡ |
| **Time to over-anticoagulation (INR≥4.0) (days)** | 4 | 14 | 17 | 2 | NA§ | 1 | 15 | 4 | NA§ | 10 |
| **%ITR** | 53.2 | 47.4 | 70 | 54.2 | 76.9 | 45.5 | 62.2 | 55.1 | 73.9 | 43.6 |
| **%TTR** | 69 | 62.4 | 83.9 | 62.3 | 83.4 | 45.5 | 84.4 | 71.3 | 77.9 | 38.2 |
| **Number of dose changes** | 50 | 21 | 20 | 12 | 10 | 14 | 23 | 36 | 8 | 21 |
| **Frequency of INR measurements (per month)** | 13.2 | 3.6 | 5 | 4 | 4.3 | 5.5 | 6.2 | 11.5 | 3.8 | 6.5 |
| **No. of INR values ≥ 4.0** | 11 | 5 | 2 | 2 | 0 | 2 | 5 | 6 | 0 | 2 |
| **No. of INR values ≥ 5.0** | 2 | 3 | 0 | 1 | 0 | 1 | 1 | 3 | 0 | 2 |

‡ Stable anticoagulation was not achieved in these patients.
§ Patients did not have INR measurements ≥ 4.0.

**Table 10. Descriptive statistics of the study outcomes for Group 1 case and control subjects.**

| Outcome | | N | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| **Time to first therapeutic INR (days)** | **Case** | 5 | 5 | 2 | 6 |
| | **Control** | 5 | 2 | 1 | 3 |
| **Time to stable anticoagulation (days)** | **Case** | 3 | 29 | 9 | 87 |
| | **Control** | 4 | 96.5 | 24 | 138 |
| **Time to over-anticoagulation (INR≥4.0) (days)** | **Case** | 3 | 15 | 4 | 17 |
| | **Control** | 5 | 4 | 1 | 14 |
| **%ITR** | **Case** | 5 | 70 | 53.2 | 76.9 |
| | **Control** | 5 | 47.4 | 43.6 | 55.1 |
| **%TTR** | **Case** | 5 | 83.4 | 69 | 84.4 |
| | **Control** | 5 | 62.3 | 38.2 | 71.3 |
| **Number of dose changes** | **Case** | 5 | 20 | 8 | 50 |
| | **Control** | 5 | 21 | 12 | 36 |
| **Frequency of INR measurements (per month)** | **Case** | 5 | 5 | 3.8 | 13.2 |
| | **Control** | 5 | 6.3 | 4 | 11.5 |
| **No. of INR values ≥ 4.0** | **Case** | 3 | 2 | 0 | 11 |
| | **Control** | 5 | 2 | 2 | 6 |
| **No. of INR values ≥ 5.0** | **Case** | 2 | 0 | 0 | 2 |
| | **Control** | 5 | 2 | 1 | 3 |

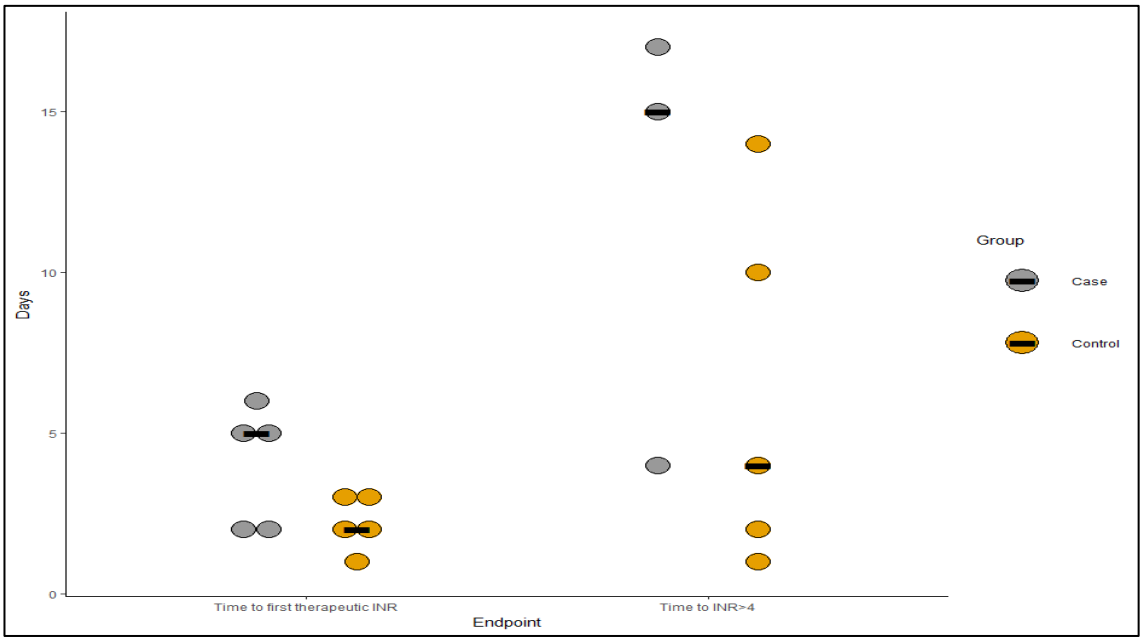


**Figure 17.** Time to first therapeutic INR and time to over-anticoagulation in Group 1 case and control subjects. Black horizontal lines represent the median values.

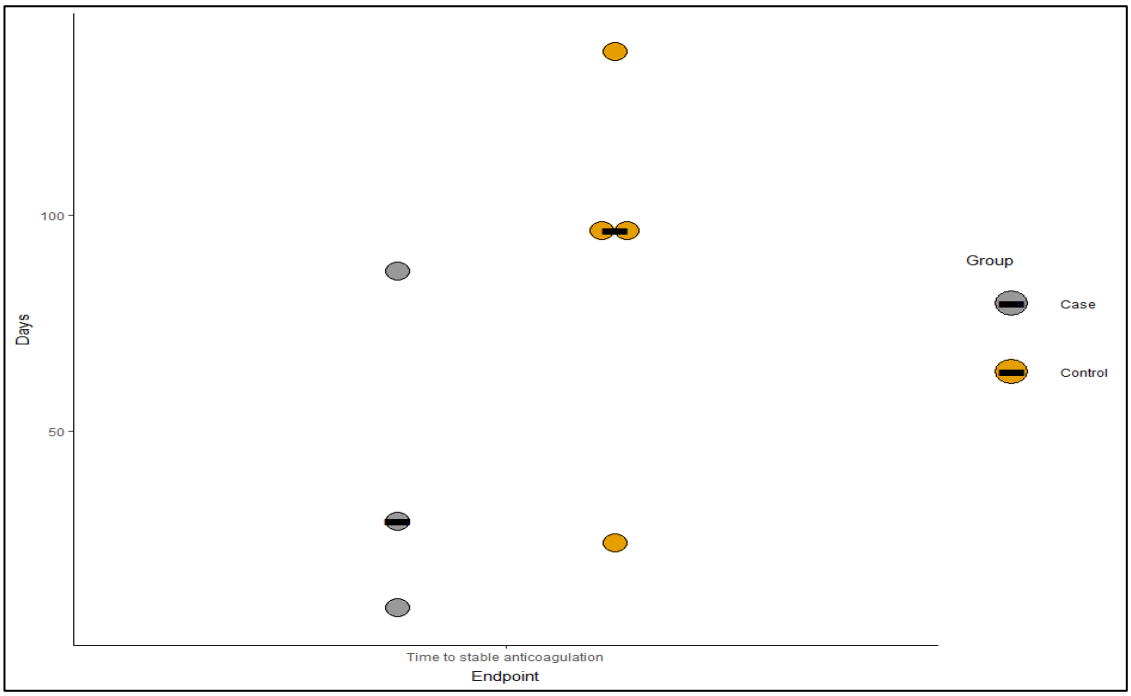


**Figure 18.** Time to stable anticoagulation in Group 1 case and control subjects. Black horizontal lines represent the median values.

#### 4.3.2.2. Time in therapeutic range

The median percentage of the INR observations within the target range (%ITR) for the case subjects was 70% whereas the median %ITR for the control subjects was 47.4%. The median percentage of time in therapeutic range (%TTR) for the case subjects was 83.4% whereas that of the control group was 62.3% (Figure 19). All the case subjects had higher %ITR and %TTR than their controls, yet due to the very small sample size, it was not appropriate to perform a statistical test to assess the significance of the difference in %ITR and %TTR between the two groups.


**Figure 19.** The percentage of INR measurements in target therapeutic range (%ITR) and percentage of time in therapeutic range (%TTR) for Group 1 case and control subjects. Black horizontal lines represent the median values.

#### 4.3.2.3. Frequency of INR measurements per month and frequency of dose alterations

The median frequency of INR measurements was 5 measurements/month for the case subjects as compared to 6.3 measurements/month for the controls. Three (out of 5) of the case subjects had lower frequency of measurements than their control subjects.

The median frequency of dose alterations was 20 for the case subjects as compared to 21 for the controls. The frequency of dose alterations was lower in three of the case subjects than their controls (Figure 20).

#### 4.3.2.4. Number of INR values ≥ 4.0 and ≥ 5.0

The median number of INR values ≥ 4.0 was 2 for both the case and the control groups. In contrast, the median of the number of INR values ≥ 5.0 was zero for the case group as compared to 2 for the control group (Figure 21).

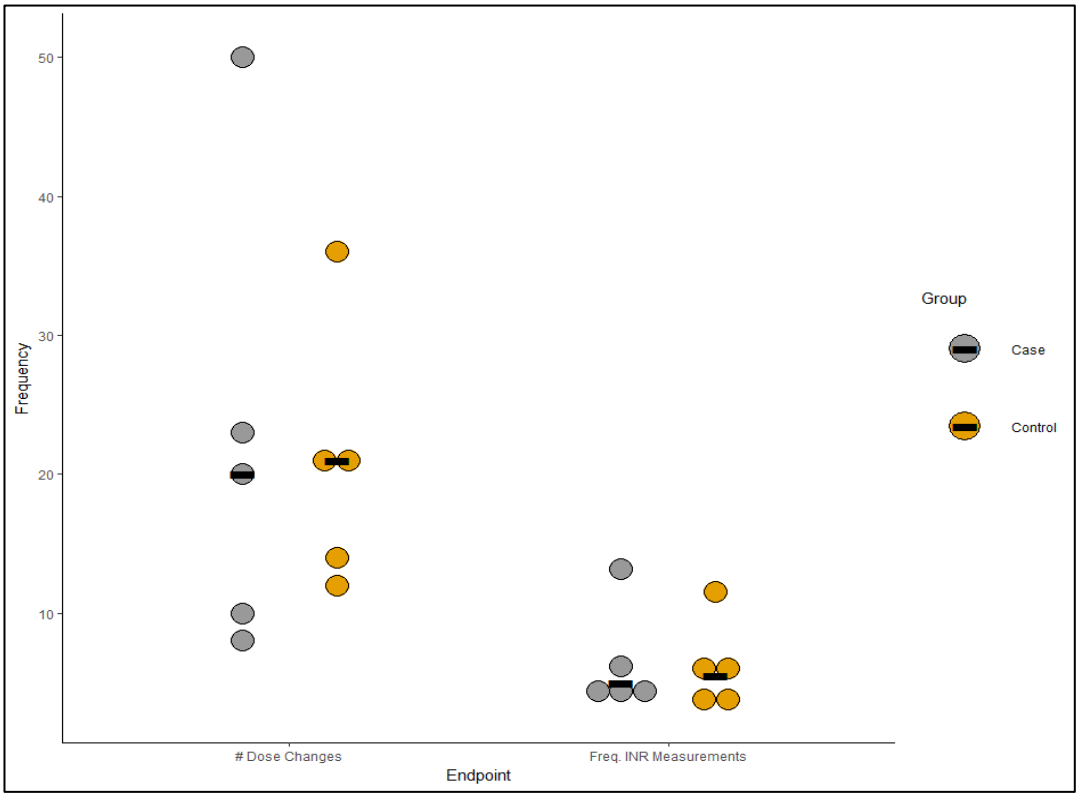


**Figure 20.** The frequency of dose changes and the frequency of INR measurements per month for Group 1 case and control subjects. Black horizontal lines represent the median values.

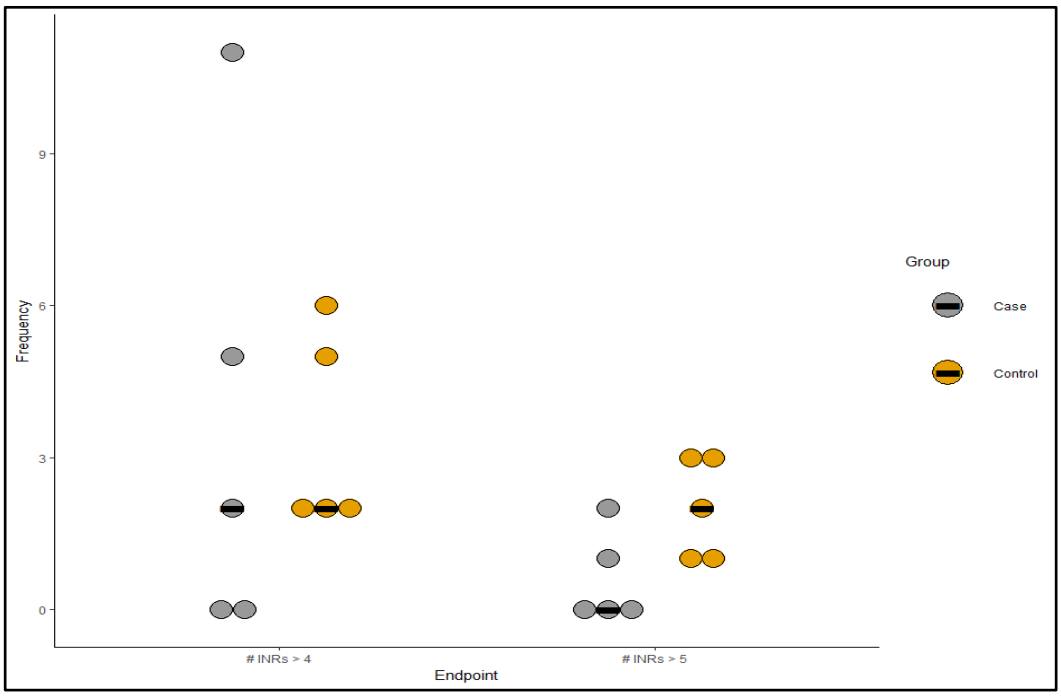


**Figure 21.** Over-anticoagulation in Group 1 case and control subjects. Black horizontal lines represent the median values.

#### 4.3.2.5. Minor bleeding events

Only two symptom diary cards were received back from the families. There were no minor bleeding events recorded in these cards. The first card was for case 1, aged 5.4 years, who was taking warfarin for a mechanical heart valve (MVR) with a target INR range of 2.5-3.5. The second card was for case 5, aged 8.9 years, who was receiving warfarin therapy after a Fontan procedure.

#### 4.3.2.6. Concomitant medications used

The medications used in the post-operative period was comparable between the case and control groups. These included medications like antibiotics, analgesics, diuretics, angiotensin converting enzyme (ACE) inhibitors and medications for post-operative gastrointestinal symptoms. The most common concomitant medications prescribed upon discharge from the hospital were diuretics including furosemide and spironolactone in addition to other drugs like insulin, digoxin, amiodarone, propranolol, sildenafil and lisinopril that were prescribed for particular patients/controls. These medications do not have a potential interaction with warfarin apart from amiodarone which can increase the anticoagulant effects of warfarin. Amiodarone was used in control number 4 in whom the %ITR was 55.1% and %TTR was 71.3% as compared to 62.2% and 84.4% for case number 4, respectively. However, the exact date of stopping amiodarone treatment could not be obtained, therefore, the lower %ITR and %TTR for this patient could not only be attributed to amiodarone use. In addition, warfarin is usually closely monitored in the post-operative period which can help to overcome any problems resulting from potential drug interactions.

#### 4.3.2.7. Assessment of extremely above- and below-range INR measurements

To assess the extreme above-range INR measurements, the number of occasions where warfarin treatment was withheld and/or vitamin K was used was estimated. Warfarin treatment was withheld in 4 control subjects on 5 occasions, including one occasion when vitamin K was also used compared to none in the case group.

Similarly, to assess extreme below-range INR measurements, the number of occasions where intravenous (IV) heparin or low molecular weight heparin (LMWH) was used was also estimated. IV heparin was used in two case subjects on one occasion for each of them compared to two occasions of IV heparin use in one control subject and one occasion of LMWH use in another control subject.

#### 4.3.2.8. Missed and overridden doses

From a total of 218 INR measurements, missed dosing occurred on 6 occasions (2.8%). In addition, there were 4 occasions of dose overriding out of a total of 212 dose recommendations made by the model (1.9%) in Group 1 patients.

### 4.4. Discussion

This study has evaluated, for the first time, on a prospective basis, warfarin dose management in children using the model-based approach. Dosing management involved both initial doses as well as dose adjustments made after every INR feedback obtained from the patients. The results of this study have shown that model-based warfarin dosing has resulted in a longer time to reach a therapeutic INR. However, there was a greater percentage of INR measurements within the target therapeutic range and also a greater percentage of time within this range when compared to the traditional dosing approach.

In addition, model-based warfarin dosing has resulted in a desirable longer period of time before over-anticoagulation occurred and there were fewer over-anticoagulated patients and a shorter time to reach stable anticoagulation when compared with the traditional dosing approach.

The median time to first therapeutic INR was longer for the case subjects as compared to the controls (median 5 days vs 2 days). This was due to the difference between the two dosing approaches. The usual clinical practice is to start with a loading dose of 0.1-0.2 mg/kg (maximum 10 mg) which may be repeated if the subsequent INR value is between 1.1-1.4 (Appendix 1). In contrast, the model predicts the initial warfarin dose based on typical population parameter estimates and the individual patient's covariates (age, weight and CYP2C9 and VKORC1 genotypes). Subsequent dose adjustments are made after the INR feedback is obtained from the patient (Chapter 2, Section 2.2). In addition, there was one patient (case 4) with mechanical mitral valve and target INR range of 2.5-3.5 who attained the target therapeutic INR after 5 days as compared to 3 days for the control. This patient started warfarin treatment at a lower target (2.0-3.0) because there was a risk of bleeding. This target range was attained after 2 days of treatment when it was then changed to 2.5-3.5 and the patient required further 3 days of treatment to attain the new target range. Therefore, this has also affected the result of time to first therapeutic INR for the case subjects. Also, the loading dose approach was found to be associated with high above-range INR values for two of the control subjects. The INR values after loading doses were 7.1 and 5.4 for control 2 and 3, respectively. The results obtained for the time to first therapeutic INR in this research study are comparable to that demonstrated by Tabib and colleagues' study (Tabib et al., 2015). The mean time to first

therapeutic INR was 3.4 days (SD 1.2) in the genotype guided group as compared to 3.5 days (SD 1.4) in the standard dosing arm.

The model-based approach to warfarin dosing resulted in longer time to over-anticoagulation (median 15 vs 4 days) and fewer over-anticoagulated patients (3 vs 5) as compared to the controls. This may be due to the model's dose estimation approach where the dose is adjusted based on the mean of the target INR range (Chapter 2, Section 2.2). This can help to obtain better anticoagulation control by minimising the supra-therapeutic INR values that can predispose to bleeding complications.

The model-based approach to warfarin dosing was shown to result in greater percentage of INR measurements in the target range (median 70% vs 47.4%) as well as greater percentage of time in therapeutic range (median 83.4% vs 62.3%) as compared to the traditional dosing approach. This can also help to obtain better anticoagulation control by minimising above and below range INR values and hence minimising the risk of bleeding and thrombosis, respectively. In adults, the genotype-guided warfarin dosing has also been shown to significantly improve the percentage of time in target therapeutic range as compared to the standard dosing approach (Pirmohamed et al., 2013). The percentage of time in target therapeutic range was 67.4% in the genotype-guided group as compared to 60.3% in the standard dosing group (Pirmohamed et al., 2013). Also, the PK/PD model-based warfarin dosing in adults was shown to result in a significant improvement in the time in the therapeutic range as compared to the pharmacogenetic/clinical based dosing (Perlstein et al., 2012). The mean time in the target therapeutic range for the pharmacogenetic/clinical algorithm was found to be 58.9% whereas that of the two PK/PD algorithms was found to be 59.7% and 65.8%, respectively (Perlstein et al., 2012).

The number of patients who achieved stable anticoagulation was comparable in the two dosing groups (3 cases vs 4 controls), however, model-based dosing has achieved stable anticoagulation faster than the traditional dosing approach (median 29 days for cases vs 96.5 days for controls). The time to stable anticoagulation achieved by model-based dosing in this study is comparable to the results obtained by Tabib et al. where the mean time to stable anticoagulation was 32.8 days (SD 6) in the genotype-guided dosing group (Tabib et al., 2015).

However, the local practice at the EMCHC is to keep the patients within an acceptable INR range rather than to strictly adhere to the prespecified target therapeutic ranges. In other words, the concern is more about how far the INR measurements are above or below the target range which can predispose to the risk of bleeding or thrombosis, respectively. This will be discussed in detail in Chapter 6. Warfarin treatment was withheld on 5 occasions in the control group, including one occasion when vitamin K was also used compared to none in the case group. Conversely, IV heparin was used on two occasions in the case group compared to two occasions of IV heparin use and one occasion of LMWH use in the control group. This may imply that model-based warfarin dosing can improve the anticoagulation control of warfarin particularly that regarding reducing the incidence of having very high INR values that can predispose to bleeding events.

The incidence of minor bleeding events could not be assessed because only two of the patients' symptom diary cards were received back from the families. However, this might imply good anticoagulation control in the remaining 3 case subjects since no bleeding events were reported.

A major limitation of the present study is that the sample size was small to enable statistically valid comparisons to be made. The low recruitment rate was due to the limited number of patients presented for cardiac surgery during the 14 months recruitment period. Only 11 candidates presented for cardiac surgery during the entire recruitment period. Nine families were approached from whom only 5 consented to participate in the study. Two of the approached patients received antiplatelet therapy with aspirin as advised by the doctors. The two other approached families did not consent to participate in the study. The parents wanted warfarin treatment to be prescribed by the doctors as their children were to start it for the first time. There were two other candidates who presented for cardiac surgery but were not approached. One candidate was not approached because the patient originally presented for heart valve repair but a decision to replace the valve was made intra-operatively. The original study protocol that was in use during that period did not allow the researcher to approach this kind of candidate because of the limited time available to obtain consent/assent. Therefore, a major amendment to the protocol was made and subsequently submitted to the Research Ethics Committee for approval in order not to miss this kind of candidate (Appendix 2). The other candidate's parent was not approached as she did not want her child to be involved in a research project.

Besides, the effect of genetic and non-genetic factors on the study outcomes and warfarin dose requirement could not be assessed. This was because of the small sample size that contained only the wild type CYP2C9 and only two patients with heterozygous VKORC1 variant allele.

The preliminary results obtained from this study have shown that model-based warfarin dosing has improved the anticoagulation control in children starting warfarin therapy for the first time after heart surgery. However, this new approach of warfarin

dosing/monitoring needs to be further explored in a larger sample size cohort to confirm these preliminary results.

# *Chapter Five*

## *The prospective clinical study*

## *(Group 2)*

# Chapter 5: The prospective clinical study: Patients maintained on warfarin treatment post-cardiac surgery (Group 2):

## 5.1. Introduction

Children with congenital heart disease who require long-term warfarin treatment need to be closely monitored to avoid both thromboembolic and bleeding complications. Therefore, maintenance of the target INR range is pivotal to ensure the safety and effectiveness of warfarin treatment (Giglia et al., 2013). However, maintaining the target therapeutic INR is intensely challenging because of various factors that affect the drug's PK and PD and hence affecting both the dose requirements and response to the drug. For this reason, it is crucial to individualise warfarin dosing in order to optimise its anticoagulant control.

Population PK/PD models for individualising warfarin dosing have been developed and evaluated in children (Hamberg et al., 2013; Lala et al., 2013). However, these models were never tested clinically, on a prospective basis to assess their clinical utility. This research project involves, for the first time, the prospective clinical evaluation of a mechanistic PK/PD model (Hamberg et al., 2015) in children maintained on warfarin treatment after congenital heart surgery.

## 5.2. Methodology

See Chapter 2 Section 2.4.

## 5.3. Results

### 5.3.1. Patient characteristics

Patient recruitment occurred between October 2015 and August 2016. Forty-eight patients were screened, 29 patients were enrolled in the study from whom 26 patients completed the follow up period and were included in the analysis. One patient died because of deterioration of his medical condition, one patient's mother withdrew consent and one patient was withdrawn from the study because his warfarin treatment was stopped following replacement of his mechanical heart valve with a bioprosthetic valve. The characteristics of Group 2 patients are summarised in Table 11. The mean patients' age was 9.01 years (SD 4.8) and the median weight was 24.9 kg. Most of the patients were males (69.2%) and the majority were of the White ethnicity (76.9%). The wild type CYP2C9 genotype was predominant (61.5%) whereas more than half of the patients were carriers of the heterozygous VKORC1 genotype (G/A) (53.8%). The most common indication for warfarin anticoagulation in this sample was Fontan procedure (76.9%). The most frequent target therapeutic INR range was 2.0-3.0 (46.2%) and the most commonly used dosage form was warfarin tablets (69.2%).

### 5.3.2. Study outcomes

A total of 1073 INR measurements were collected during both phases of treatment over a total follow up period of 26 patient years.

#### 5.3.2.1. Time in therapeutic range

The mean percentage of INR measurements in the target range (%ITR) of the model phase was 68.82%, whereas that of the Doctor phase was 67.9%. This represented a

**Table 11. Characteristics of Group 2 patients.**

| | |
|---|---|
| Age* (years), mean ± SD (range) | 9.0 ± 4.8 (1-17.3) |
| Weight (kg), median (range) | 24.9 (9.5-62.8) |
| Gender, N (%) | |
| Male<br>Female | 18 (69.2)<br>8 (30.8) |
| Ethnicity, N (%) | |
| White<br>Asian<br>Other§ | 20 (76.9)<br>4 (15.4)<br>2 (7.7) |
| CYP2C9 genotype, N (%) | |
| *1/*1<br>*1/*2<br>*1/*3<br>Missing | 16 (61.5)<br>6 (23.1)<br>3 (11.5)<br>1 (3.8) |
| VKORC1 genotype, N (%) | |
| G/G<br>G/A | 12 (46.2)<br>14 (53.8) |
| Indication for warfarin, N (%) | |
| Fontan<br>MVR<br>AVR | 20 (76.9)<br>5 (19.2)<br>1 (3.8) |
| Target INR range, N (%) | |
| 2.0-3.0<br>1.5-2.5<br>2.5-3.5<br>Other† | 12 (46.2)<br>7 (26.9)<br>4 (15.4)<br>3 (11.5) |
| Dosage form used, N (%) | |
| Liquid<br>Tablet (swallowed whole)<br>Tablet (swallowed whole but halved for 0.5 mg)<br>Tablet (crushed & mixed with water) | 8 (30.8)<br>7 (26.9)<br>7 (26.9)<br><br>4 (15.4) |
| Total number of patients (%) | 26 (100) |

* Age at enrolment.
§ Other: one patient mixed White and Black, one patient mixed White and Asian.
† Other: one patient 1.8-3.0, one patient 2.0-2.5, one patient 3.0-4.0.
MVR mitral valve replacement.
AVR aortic valve replacement.

mean difference in %ITR between the Model phase and the Doctor phase of 0.92% (p=0.84). The mean percentage of time in target range (%TTR) of the Model phase was 85.47% as compared to that of the Doctor phase, 80.2%. The mean difference in %TTR between the Model phase and the Doctor phase was 5.27% (p = 0.09) (Table 12).

**Table 12. Time in therapeutic range (measured as %ITR and %TTR), frequency of INR measurements and frequency of dose alterations of Group 2 patients.**

| Outcome | N | Model phase | Doctor phase | Mean difference (95% Confidence Interval)† | p-value |
|---|---|---|---|---|---|
| **%ITR, mean (SD)** | 26 | 68.82 (19.8) | 67.9 (23.19) | 0.92 (-8.25, 10.09) | 0.84‡ |
| **%TTR, mean (SD)** | 26 | 85.47 (13.03) | 80.2 (17.99) | 5.27 (-0.78, 11.32) | 0.09‡ |
| **%ITR (excluding 5 cases), mean (SD)** | 21 | 71.28 (20.86) | 65.51 (23.3) | 5.77 (-3.82, 15.35) | 0.22‡ |
| **%TTR (excluding 5 cases), median (IQR)** | 21 | 91.8 (73.9-97.3) | 77.3 (65.4-94.3) | -- | 0.03§ |
| **Frequency of INR measurements (per month), median (IQR)** | 26 | 2.3 (1.78-4.23) | 1.9 (1.3-3.05) | -- | 0.08§ |
| **Frequency of dose alterations, median (IQR)** | 26 | 6.5 (3 - 15.25) | 2.5 (1 - 9.75) | -- | 0.02§ |

† Values are the mean difference between the Model phase and the Doctor phase.
‡ Paired sample t-test.
§ Wilcoxon test.
%ITR is the percentage of INR measurements in therapeutic range.
%TTR is the percentage of time in therapeutic range.
IQR is the interquartile range.

However, there were five patients who underwent procedures (cardiac catheterization or dental procedure) and/or experienced periods of illness in one of the treatment phases and where warfarin treatment was stopped and then resumed afterwards which may have resulted in a biased comparison between the two phases. Therefore, an additional analysis was performed after excluding these five cases. The mean %ITR of the Model phase was

71.28% whereas that of the Doctor phase was 65.51%. The mean difference in %ITR between the Model phase and the Doctor phase was 5.77% (p = 0.22). Whereas the %TTR of the Model phase was significantly higher than that of the Doctor phase (median %TTR Model phase 91.8%, Doctor phase 77.3 %, p = 0.03) (Table 12). In Table 13 is shown the time within therapeutic range of these five patients for the two treatment phases. The medical issues occurred in the Doctor phase in patient number 1 whereas they occurred in the Model phase for the remaining patients.

**Table 13. The time in therapeutic range expressed as %ITR and %TTR of the two treatment phases for the patients with medical issues.**

| Patient ID | %ITR | | %TTR | |
|---|---|---|---|---|
| | Model phase | Doctor phase | Model phase | Doctor phase |
| 1 | 47.6 | 40.6 | 57 | 48.8 |
| 7 | 69.6 | 85.7 | 86 | 94.9 |
| 10 | 50 | 80 | 80.2 | 94.1 |
| 23 | 56 | 100 | 79.7 | 100 |
| 27 | 69.2 | 83.3 | 92.7 | 98.4 |

### 5.3.2.2. Sensitivity analysis of the time in therapeutic range of the Model and Doctor phases

#### A- Age and weight sub-groups

Patients were stratified into 3 age groups, 1-5, 6-10 and 11-18 years, and into 3 weight groups, ≤ 20, 21-40, and > 40 kg. The results of the analysis are demonstrated in Table 14.

**Table 14. Time in therapeutic range (%ITR and %TTR) in Group 2 patients stratified into age and weight groups.**

| | Number of patients | Model phase | Doctor phase | Mean difference (95% Confidence Interval)† | p-value§ |
|---|---|---|---|---|---|
| **Age groups (year)** | | | | | |
| **1-5** | | | | | |
| **%ITR, mean (SD)** | 10 | 57.77 (14.3) | 59.72 (23.1) | -1.95 (-16.88, 12.98) | 0.77 |
| **%TTR, mean (SD)** | 10 | 77.98 (12.66) | 73.18 (20.66) | 4.8 (-4.76, 14.36) | 0.29 |
| **6-10** | | | | | |
| **%ITR, mean (SD)** | 6 | 77.23 (15.05) | 68.02 (27.34) | 9.22 (-12.52, 39.95) | 0.48 |
| **%TTR, mean (SD)** | 6 | 92.17 (7.31) | 81.17 (19.21) | 11 (-11.24, 33.24) | 0.26 |
| **11-18** | | | | | |
| **%ITR, mean (SD)** | 10 | 74.81 (23.15) | 76 (19.96) | -1.19 (-16.53, 14.15) | 0.87 |
| **%TTR, mean (SD)** | 10 | 88.95 (13.25) | 86.65 (12.88) | 2.3 (-6.83, 11.43) | 0.58 |
| **Weight groups (kg)** | | | | | |
| **≤ 20** | | | | | |
| **%ITR, mean (SD)** | 11 | 63.66 (14.4) | 61.45 (25.85) | 2.21 (-14.29, 18.70) | 0.77 |
| **%TTR, mean (SD)** | 11 | 80.56 (13.79) | 73.34 (21.87) | 7.22 (-4.04, 18.48) | 0.18 |
| **21-40** | | | | | |
| **%ITR, mean (SD)** | 7 | 72.87 (22.77) | 73.24 (22.87) | -0.37 (-20.62, 19.88) | 0.97 |
| **%TTR, mean (SD)** | 7 | 91.34 (8.12) | 87.21 (14.51) | 4.13 (-9.69, 17.95) | 0.49 |
| **> 40** | | | | | |
| **%ITR, mean (SD)** | 8 | 72.36 (24.23) | 72.09 (20.11) | 0.28 (-19.60, 20.15) | 0.98 |
| **%TTR, mean (SD)** | 8 | 87.1 (14.23) | 83.51 (12.53) | 3.59 (-8.16, 15.34) | 0.49 |

† Values are the mean difference between the Model phase and the Doctor phase.
§ Paired sample t-test.
%ITR is the percentage of INR measurements in therapeutic range.
%TTR is the percentage of time in therapeutic range.

The %ITR of the Model phase tended to be higher than that of the Doctor phase in the 6-10 years age group only but this was not statistically significant ($p = 0.48$). The trend for %TTR in the Model phase was higher than that of the Doctor phase in all age groups but this was not statistically significant (Table 14 and Figure 22).

The %ITR of the Model phase was higher for the weight groups ≤ 20 kg and > 40 kg although, again, these differences were not statistically significant ($p = 0.77$ and 0.98, respectively). The trend for %TTR in the Model phase was higher than that of the Doctor phase in all weight groups but this was not statistically significant (Table 14).

**B- Indication sub-groups**

The patients were also grouped according to the indication of warfarin treatment into those with Fontan procedure and those with mechanical heart valves. The analysis of the indication group was performed before and after excluding the cases who experienced medical issues during either phase of treatment. The results are summarised in Table 15. The %ITR of the Model phase for Fontan patients was higher than that of the Doctor phase before and after the exclusion of the cases with medical issues but this was not statistically significant ($p = 0.74$ and 0.25, respectively). The %TTR during the Doctor phase was statistically significantly higher than that during the Model phase ($p<0.05$). However, after excluding the 5 cases with medical issues, the %TTR during the Model phase was statistically significantly higher than that during the Doctor phase ($p = 0.02$) (Figure 22).

For patients with mechanical heart valves, the %ITR of the Model phase was higher than that of the Doctor phase after excluding the 5 cases with medical issues although

**Table 15. Time in therapeutic range (%ITR and %TTR) in Group 2 patients grouped according to the indication of warfarin and the target therapeutic range.**

| | Number of patients | Model phase | Doctor phase | Mean difference (95% Confidence Interval)† | p-value§ |
|---|---|---|---|---|---|
| **Indication** | | | | | |
| **Fontan procedure** | | | | | |
| **%ITR, mean (SD)** | 20 | 73.22 (19.76) | 71.38 (22.90) | 1.84 (-9.58, 13.26) | 0.74 |
| **%TTR, mean (SD)** | 20 | 72.3 (17.57) | 89.74 (9.87) | -17.45 (-22.86, -12.03) | < 0.05 |
| **%ITR cases with issues excluded, mean (SD)** | 17 | 74.68 (21) | 68.15 (23.21) | 6.53 (-5.15, 18.21) | 0.25 |
| **%TTR cases with issues excluded, mean (SD)** | 17 | 90.38 (10.37) | 80.9 (16.04) | 9.48 (1.79, 17.16) | 0.02 |
| **Mechanical valves** | | | | | |
| **%ITR, mean (SD)** | 6 | 54.15 (11.84) | 56.3 (22.08) | -2.15 (-20.38, 16.08) | 0.77 |
| **%TTR, mean (SD)** | 6 | 71.25 (12.75) | 69.45 (21.61) | 1.8 (-10.46, 14.06) | 0.72 |
| **%ITR cases with issues excluded, mean (SD)** | 4 | 56.83 (14.29) | 54.3 (23.19) | 2.53 (-19.24, 24.29) | 0.74 |
| **%TTR cases with issues excluded, mean (SD)** | 4 | 72.58 (13.20) | 68.45 (20.81) | 4.13 (-13.62, 21.87) | 0.51 |
| **Target INR range** | | | | | |
| **1.5-2.5** | | | | | |
| **%ITR, mean (SD)** | 7 | 84.51 (17.17) | 74.96 (21.42) | 9.56 (-12.02, 31.13) | 0.51 |
| **%TTR, mean (SD)** | 7 | 93.03 (8.32) | 86.44 (15.78) | 6.59 (-10.64, 23.81) | 0.39 |
| **2.0-3.0** | | | | | |
| **%ITR, mean (SD)** | 12 | 64.46 (19.89) | 70.44 (21.78) | -5.98 (-20.19, 8.23) | 0.37 |
| **%TTR, mean (SD)** | 12 | 86.31 (10.75) | 83 (15.55) | 3.31 (-5.73, 12.34) | 0.44 |
| **2.5-3.5** | | | | | |
| **%ITR, mean (SD)** | 4 | 55.83 (14.9) | 54.68 (22.87) | 1.15 (-18.86, 21.16) | 0.87 |
| **%TTR, mean (SD)** | 4 | 69.53 (15.46) | 67.2 (22.09) | 2.33 (-12.19, 16.84) | 0.65 |
| **Other** | | | | | |
| **%ITR, mean (SD)** | 3 | 66.93 (13.66) | 58.87 (35.63) | 8.07 (-78.04, 94.18) | 0.73 |
| **%TTR, mean (SD)** | 3 | 85.77 (14.35) | 71.8 (24.73) | 13.97 (-33.46, 61.39) | 0.33 |

† Values are the mean difference between the Model phase and the Doctor phase.
§ Paired sample t-test.
%ITR is the percentage of INR measurements in therapeutic range.
%TTR is the percentage of time in therapeutic range.

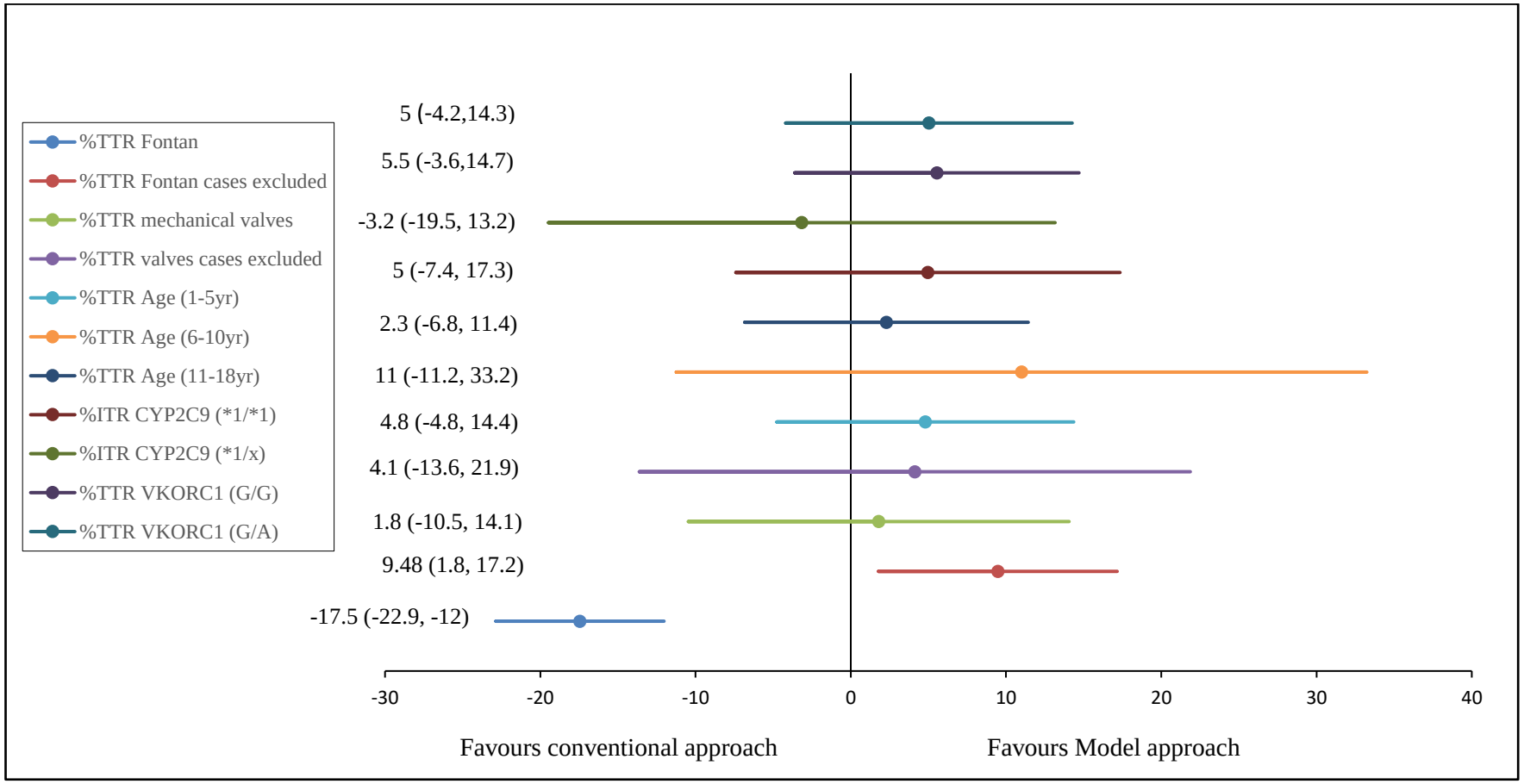


**Figure 22. Forest plot of the time in therapeutic range of the Model and Doctor phases for Group 2 patients.** Patients were sub grouped according to age, indication and genotype subgroups. The mean differences (95% confidence intervals) are shown for each subgroup. The %TTR was used for the indication, age and VKORC1 subgroups whereas the %ITR was used for the CYP2C9 subgroup (because %TTR data was not normally distributed).

statistical significance was not achieved (p = 0.74). Similarly, the %TTR of the Model phase was higher both before and after excluding the cases with medical issues (p = 0.72 and 0.51, respectively) (Figure 22).

**C- Target INR range sub-groups**

For the target INR ranges, the %ITR of the Model phase was higher for the 1.5-2.5 range (p = 0.51), the 2.5-3.5 range p = 0.87) and for the other target ranges (p = 0.73). The %TTR of the Model phase was higher than that of the Doctor phase for all target INR ranges. However, none of these differences were statistically significant (Table 15).

**D- CYP2C9 and VKORC1 sub-groups**

The patients were also grouped according to CYP2C9 genotype (*1/*1 vs *1/*2 and *1/*3) and VKORC1 genotype (G/G vs G/A). The results of the analysis are summarised in Table 16. The %ITR of the Model phase was higher than that of the Doctor phase in the wild genotype (*1/*1) (p = 0.41). The median %TTR of the Model phase was higher than that of the Doctor phase (p = 0.1) for the *1/*1 genotype. The %TTR of the Model phase for the variant alleles (*1/*2 and *1/*3) was also higher than that of the Doctor phase. However, none of these differences was statistically significant (p =0.8).

For VKORC1 genotypes, the %ITR of the Model phase was higher than that of the Doctor phase for both G/G and G/A genotypes (p = 0.8 and 0.97, respectively). The %TTR of the Model phase for both genotypes was also higher than that of the Doctor phase with p = 0.21 for G/G genotype and p = 0.26 for G/A genotype (Figure 22). Though, these differences were not statistically significant.

**Table 16. Time in therapeutic range (%ITR and %TTR) in Group 2 patients grouped according to the CYP2C9 and VKORC1 genotypes.**

| | Number of patients | Model phase | Doctor phase | Mean difference (95% Confidence Interval)† | p-value |
|---|---|---|---|---|---|
| **CYP2C9 genotype** | | | | | |
| ***1/*1** | | | | | |
| **%ITR, mean (SD)** | 16 | 74.63 (16.99) | 69.66 (24) | 4.97 (-7.40, 17.34) | 0.41§ |
| **%TTR, median (IQR)** | 16 | 92.35 (81.28-98.4) | 87.55 (64.70-97.8) | -- | 0.1‡ |
| ***1/*2, *1/*3** | | | | | |
| **%ITR, mean (SD)** | 9 | 62.08 (20.83) | 65.23 (24.19) | -3.16 (-19.47, 13.16) | 0.67§ |
| **%TTR, mean (SD)** | 9 | 79.12 (14.91) | 78.06 (19.46) | 1.07 (-8.08, 10.21) | 0.8§ |
| **VKORC1 genotype** | | | | | |
| **G/G** | | | | | |
| **%ITR, mean (SD)** | 12 | 62.35 (17.36) | 60.66 (20.35) | 1.69 (-12.41, 15.79) | 0.8§ |
| **%TTR, mean (SD)** | 12 | 80.72 (13.93) | 75.18 (17.98) | 5.54 (-3.61, 14.7) | 0.21§ |
| **G/A** | | | | | |
| **%ITR, mean (SD)** | 14 | 74.36 (20.67) | 74.1 (24.38) | 0.26 (-13.57, 14.09) | 0.97§ |
| **%TTR, mean (SD)** | 14 | 89.55 (11.1) | 84.51 (17.49) | 5.04 (-4.19, 14.26) | 0.26§ |

† Values are the mean difference between the Model phase and the Doctor phase.
§ Paired sample t-test.
‡ Wilcoxon test.
%ITR is the percentage of INR measurements in therapeutic range.
%TTR is the percentage of time in therapeutic range.
IQR is the interquartile range.

## E- Dosage form sub-groups

The patients were also stratified according to the dosage form used into liquid and tablet groups. The results of the analysis are shown in Table 17. The %ITR of the Model

phase was higher than that of the Doctor phase in the tablet group (p = 0.78). In contrast, the %TTR of the Model phase was higher than that of the Doctor phase for both the liquid group and the tablet group (p = 0.25 and 0.19, respectively). Though, none of these differences was statistically significant.

**Table 17. Time in therapeutic range (%ITR and %TTR) in Group 2 patients stratified according to the dosage form used.**

| | Number of patients | Model phase | Doctor phase | Mean difference (95% Confidence Interval)† | p-value§ |
|---|---|---|---|---|---|
| **Liquid** | | | | | |
| **%ITR, mean (SD)** | 8 | 66.8 (21.87) | 67.68 (22.28) | -0.88 (-12.84, 11.09) | 0.87 |
| **%TTR, mean (SD)** | 8 | 84.3 (13.75) | 79.19 (18.28) | 5.11 (-4.56, 14.78) | 0.25 |
| **Tablet** | | | | | |
| **%ITR, mean (SD)** | 18 | 69.71 (19.41) | 67.99 (24.22) | 1.72 (-11.17, 14.61) | 0.78 |
| **%TTR, mean (SD)** | 18 | 85.99 (13.07) | 80.66 (18.38) | 5.34 (-2.90, 13.58) | 0.19 |

† Values are the mean difference between the Model phase and the Doctor phase.
§ Paired sample t-test.
%ITR is the percentage of INR measurements in therapeutic range.
%TTR is the percentage of time in therapeutic range.

### 5.3.2.3. Frequency of INR measurements per month

The frequency of INR measurements per month of the Model phase was slightly higher than that of the Doctor phase. The median of INR measurements was 2.3 measurements/month for the Model phase and 1.9 measurements/month for the Doctor phase (p = 0.08) (Table 12).

### 5.3.2.4. Frequency of dose alterations

The frequency of dose alterations of the Model phase was statistically significantly higher than that of the Doctor phase (median 6.50 for the Model phase and 2.5 for the Doctor phase, p = 0.02) (Table 12). Patients were grouped according to the indication of warfarin treatment into those with Fontan procedure and those with mechanical heart valves. The number of dose changes of the Doctor phase was lower than that of the Model phase for both indications (p = 0.08 and p = 0.53 respectively) (Table 18). The number of dose changes of the Model phase was also higher than that of the Doctor phase for the target INR ranges 1.5-2.5, 2.0-3.0, and 2.5-3.5 (p = 0.56, p = 0.02 and p = 0.26, respectively). In contrast, there was a trend, though not statistically significant, for the number of dose changes during the Model phase to be lower than that of the Doctor phase for other target INR ranges (p = 0.47) (Table 18).

**Table 18. Number of dose alterations in Group 2 patients grouped according to the indication of warfarin and the target therapeutic range.**

| | Number of patients | Model phase | Doctor phase | Mean difference (95% Confidence Interval)† | p-value§ |
|---|---|---|---|---|---|
| **Indication** | | | | | |
| **Fontan procedure, mean (SD)** | 20 | 6.3 (4.66) | 3.65 (4.09) | 2.65 (-0.36, 5.66) | 0.08 |
| **Mechanical valves, mean (SD)** | 6 | 31.33 (25.99) | 25.5 (20.46) | 5.83 (-16.13, 27.8) | 0.53 |
| **Target INR range** | | | | | |
| **1.5-2.5, mean (SD)** | 7 | 6.14 (5.15) | 4.14 (4.81) | 2 (-5.83, 9.83) | 0.56 |
| **2.0-3.0, mean (SD)** | 12 | 7.33 (5.26) | 3 (3.54) | 4.33 (0.73, 7.94) | 0.02 |
| **2.5-3.5, mean (SD)** | 4 | 38 (30.69) | 26 (18.13) | 12 (-15.47, 39.47) | 0.26 |
| **Other, mean (SD)** | 3 | 10.33 (9.45) | 19 (25.51) | -8.67 (-51.28, 33.95) | 0.47 |
| † Values are the mean difference between the Model phase and the Doctor phase.<br>§ Paired sample t-test. | | | | | |

### 5.3.2.5. Over-anticoagulation (INR ≥ 4.0 and ≥ 5.0)

The number of INR measurements that were ≥ 4.0 and ≥ 5.0 was compared between the Model phase and the Doctor phase. There was no statistically significant difference between the two phases of treatment in the number of INR values ≥ 4.0 (p = 0.9) and those ≥ 5.0 (p = 0.8). Summary statistics of the INR values ≥ 4.0 and ≥ 5.0 of the Model phase and Doctor phase are shown in Table 19.

**Table 19. Descriptive Statistics and p-values for INR ≥4.0 and ≥5.0 for Group 2 patients.**

| | Mean (SD) | Minimum | Maximum | Interquartile range | | |
|---|---|---|---|---|---|---|
| | | | | 25th | (Median) | 75th |
| **INR ≥ 4 Model phase†** | 2.5 (5.26) | 0 | 22 | 0 | 0 | 2 |
| **INR ≥ 4 Doctor phase†** | 3.08 (7.04) | 0 | 29 | 0 | 0 | 1.25 |
| **INR ≥ 5 Model phase§** | 0.69 (1.76) | 0 | 8 | 0 | 0 | 0 |
| **INR ≥ 5 Doctor phase§** | 0.92 (2.54) | 0 | 11 | 0 | 0 | 0 |
| † p-value = 0.9, Wilcoxon test.<br>§ p-value = 0.8, Wilcoxon test. | | | | | | |

The 26 patients were stratified based on the indication of warfarin treatment into those with Fontan procedure (N=20) and those with mechanical heart valves (N=6). Summary statistics of over-anticoagulation for patients grouped according to the indication of warfarin and the target INR ranges are shown in Table 20. For Fontan patients, the maximum number of INR values ≥ 4.0 was similar for both treatment phases, whereas the maximum number of INR values ≥ 5.0 of the Model phase was lower than that of the Doctor phase, however these were not statitistically significant (p = 0.96 and p = 1.0, respectively). For patients with mechanical heart valves, the maximum number of INR values ≥ 4.0 and the maximum number of INR values ≥ 5.0 of the Model phase were lower than those of the Doctor phase, althought this was not statistically significant (p =

**Table 20. Over-anticoagulation for the 26 patients in Group 2 patients grouped according to the indication of warfarin and the target therapeutic range.**

| | N♯ | Model phase | | | Doctor phase | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | Mean (SD) | Minimum | Maximum | Mean (SD) | Minimum | Maximum | |
| **Indication** | | | | | | | | |
| **Fontan procedure** | | | | | | | | |
| **INR ≥ 4.0** | 20 | 0† | 0 | 4 | 0† | 0 | 4 | 0.96‡ |
| **INR ≥ 5.0** | 20 | 0† | 0 | 3 | 0† | 0 | 1 | 1.0‡ |
| **Mechanical valves** | | | | | | | | |
| **INR ≥ 4.0** | 6 | 9 (8.3) | 0 | 22 | 11.67 (11.36) | 0 | 29 | 0.44§ |
| **INR ≥ 5.0** | 6 | 2.5 (2.95) | 0 | 8 | 3.67 (4.5) | 0 | 11 | 0.49§ |
| **Target INR range** | | | | | | | | |
| **1.5-2.5** | | | | | | | | |
| **INR ≥ 4.0** | 7 | 0.57 (0.79) | 0 | 2 | 0.71 (1.5) | 0 | 4 | 0.82§ |
| **INR ≥ 5.0** | 7 | 0† | 0 | 0 | 0† | 0 | 1 | 0.16‡ |
| **2.0-3.0** | | | | | | | | |
| **INR ≥ 4.0** | 12 | 0.67 (1.23) | 0 | 4 | 0.33 (0.65) | 0 | 2 | 0.46§ |
| **INR ≥ 5.0** | 12 | 0† | 0 | 3 | 0† | 0 | 0 | 0.32‡ |
| **2.5-3.5** | | | | | | | | |
| **INR ≥ 4.0** | 4 | 10.25 (9.74) | 0 | 22 | 10.25 (8.18) | 0 | 19 | 1.0§ |
| **INR ≥ 5.0** | 4 | 3 (3.46) | 0 | 8 | 2.75 (3.2) | 0 | 6 | 0.85§ |
| **Other** | | | | | | | | |
| **INR ≥ 4.0** | 3 | 4 (6.08) | 0 | 11 | 10 (16.46) | 0 | 29 | 0.42§ |
| **INR ≥ 5.0** | 3 | 0† | 0 | 3 | 0† | 0 | 11 | 0.32‡ |

† Median.
‡ Wilcoxon test.
§ Paired sample t-test.
♯ N represents the number of patients considered in each subgroup.

0.44 and p = 0.49, respectively). The maximum number of INR values ≥ 4.0 and the maximum number of INR values ≥ 5.0 for other target INR ranges was lower for the Model phase compared to the Doctor phase, however, this was not statistically significant (p = 0.42 and p = 0.32, respectively).

#### 5.3.2.6. Minor bleeding events

Only 8 symptom diary cards were received back from the families. Four families reported no bleeding events in the entire 12-month period of follow up. For the remaining 4 cards received, the minor bleeding events were as follows:

Patient number 2 experienced 5 episodes of excessive bruising from a cut during the Model phase. Two of these episodes lasted for 1 minute and the duration of the remaining episodes was not reported. No action was required for these events. This patient was in the target INR range 100% of the time during the Model phase.

Patient number 3 experienced 2 episodes of excessive bruising from a cut and 1 episode of prolonged bleeding after tooth loss during the Doctor phase. The duration of bleeding, as reported by the parent, was one week for the episodes of excessive bruising and 40 minutes for the bleeding episode after tooth loss. No action was required except in one of excessive bruising episodes where the patient was checked at the Accident and Emergency department. The INR measurements obtained around the dates specified for these events were within the target range for two of the events and slightly above the target range for the remaining event.

Patient number 15 experienced 5 episodes of nose bleeds and 1 episode of excessive bruising from a cut during the Model phase. The nose bleeds lasted from 5-90 minutes as reported by the parent whereas the duration of the bruising episode was not reported. No

action was required for any of the reported episodes. The INR measurements obtained around the dates specified for these events were all within the target range.

Patient number 28 experienced 2 episodes of nose bleeds during the Model phase. One of the episodes lasted for 5 minutes and the duration of the other episode was not reported by the parent. No action was required for both events. The INR measurements obtained around the dates specified for the two events were within and slightly above the target range, respectively.

In addition, there was one patient, from whom the symptom diary card was not received, who experienced 2 episodes of nose bleeds and 1 episode of coughing blood during the Model phase. The bleeding episodes were reported during the routine phone calls made to report the INR measurements. The nose bleeds required cauterisation at the hospital, one of which was performed at Glenfield hospital where the consultant stated that the bleeds were not caused by warfarin but made worse by it. The INR measurements reported for these events were within the target range.

#### 5.3.2.7. Concurrent medications and intercurrent illness

Ten patients were receiving long-term medications concurrently with warfarin during both phases of treatment. The medications used and the number of patients using them were as follows: sodium valproate (1), enalapril (3), lisinopril (4), spironolactone (1), furosemide (1), bumetanide (1), digoxin (2), sotalol (1), sildenafil (1), sodium chloride (1), domperidone (1), omeprazole (3), Movicol® (1), loperamide (1), oxybutynin (1), desmopressin (1), and cephalexin (1). Of these, two medications have possible drug interactions with warfarin. Spironolactone can reduce the effects of warfarin (diuresis can increase clotting factors' concentrations) and omeprazole can cause a minor increase in

the effects of warfarin (because of inhibition of R-warfarin metabolism) (Hansten and Horn, 2008). However, these medications were used on a long-term basis and any possible interaction could be overcome by regular monitoring of the INR. Antibiotics were used for intercurrent infections in 6 patients during the Model phase, the Doctor phase or both phases of treatment. The use of antibiotics was reported during the routine phone calls to report the INR measurements, hence the exact dates for starting/stopping antibiotics could not be obtained. Intercurrent illness included cold, infections and vomiting that occurred in both phases of treatment. The INR control was variable during the periods of antibiotic use and intercurrent illness and was included in the analysis of time in therapeutic range.

#### 5.3.2.8. Assessment of extremely above- and below-range INR measurements

To assess the extreme above-range INR measurements, the number of occasions where warfarin treatment was withheld and/or vitamin K was used was estimated. Warfarin treatment was withheld in 2 patients on 1 occasion for each of them during the Model phase. In contrast, the treatment was withheld in 3 patients on 1 occasion for each of them during the Doctor phase and vitamin K was used in one of these occasions.

Similarly, to assess extreme below-range INR measurements, the number of occasions where intravenous (IV) heparin or low molecular weight heparin (LMWH) was used was also estimated. IV heparin was used in 4 patients on 6 occasions during the Model phase as compared to 3 patients on 4 occasions during the Doctor phase. LMWH was used in one patient on one occasion during the Model phase. However, this was because the teenage patient did not take his warfarin dose and consumed alcohol which led to a drop in the INR measurement.

### 5.3.2.9. Missed and overridden doses

From a total of 586 INR measurements, missed dosing occurred on 15 occasions (2.6%). In addition, there were 22 occasions of dose overriding out of a total of 571 dose recommendations made by the model (3.9%) in Group 2 patients.

### 5.3.2.10. Effect of genetic and non-genetic factors on warfarin average daily dose

The average daily warfarin dose was found to be statistically significantly correlated with age ($r= 0.64$, $p < 0.05$) (Figure 23) and weight ($r= 0.64$, $p < 0.05$). However, body weight normalised dose was found to be non-significantly negatively correlated with age ($r= -0.34$, $p = 0.09$). There was one patient who required very high average daily dose of warfarin (about 18 mg/day) (Figure 23). The subsequent analysis was performed after excluding this patients.

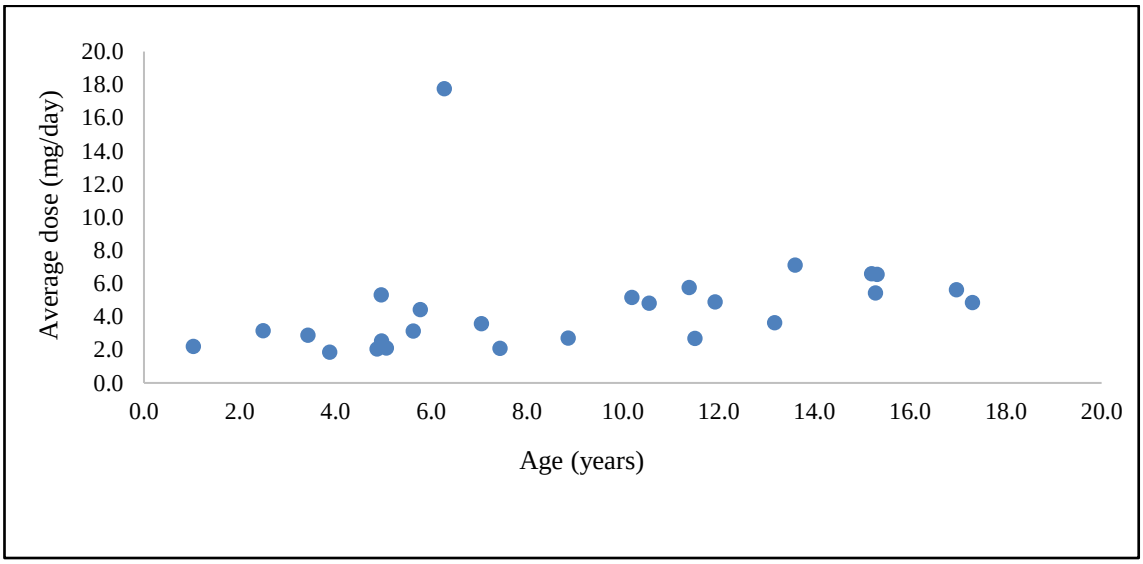


**Figure 23. Relationship between average daily warfarin dose and age**

Patients aged 1-5 years required relatively higher median daily dose of warfarin compared to older age groups; however, the difference was not statistically significant (p= 0.17). Also, male patients required higher median doses than female patients, but the difference was not statistically significant (p= 0.11). Moreover, there was no statistically significant difference in warfarin daily dose requirements for the three ethnic groups (p= 0.35) (Table 21).

Patients with VKORC1 genotype G/G required statistically significantly higher doses than those with G/A genotype (p = 0.01). The median dose for patients with wild CYP2C9 genotype (*1/*1) as well as those with variant alleles (*1/*2 and *1/*3) was similar (p =0.56).

There was a trend for patients anticoagulated for Fontan procedure to require lower warfarin doses than those anticoagulated for mechanical valves but the difference was not statistically significant (p =0.16). Similarly, patients with target INR ranges of 1.5-2.5 and 2.0-3.0 required lower median doses of warfarin compared to those with target range of 2.5-3.5 and other target ranges (p =0.07) (Table 21).

Similar results for the effect of genetic and non-genetic factors on warfarin dose were obtained after excluding the patient who required very high warfarin dose.

**5.3.2.11. Effect of genetic and non-genetic factors on time in therapeutic range**

The effect of genetic and non-genetic factors on time in therapeutic range is summarised in Table 22. Patients aged 1-5 years had the lowest time in therapeutic range compared to other age groups but this was not statistically significant (%ITR, p= 0.1, %TTR, p= 0.19). Patients with mechanical heart valves had statistically

significantly lower time within the therapeutic range than those with Fontan circulation (%ITR, p= 0.04, %TTR, p = 0.04). Patients with the target INR range of (2.5-3.5) also had the lowest time in therapeutic range compared to the other target ranges, however, this was not statistically significant (%ITR, p= 0.17, %TTR, p= 0.21). Also, patients with variant CYP2C9 variant alleles (*1/*2 and *1/*3) had lower time in therapeutic range than those with the wild genotype (*1/*1) but this was not statistically significant (%ITR, p= 0.28, %TTR, p= 0.36). In contrast, patients with the wild type VKORC1 (G/G) had lower time in therapeutic range than those with the variant allele (G/A), however, this was not statistically significant (%ITR, p= 0.08, %TTR, p= 0.11).

### 5.4. Discussion

This research project has evaluated, for the first time, on a prospective clinical basis, warfarin dose management in children using the model-based approach. Dosing management involved maintenance dose adjustments after every INR feedback obtained from the patients.

The overall comparison of the percentage of INR measurements in target range (%ITR) between the two phases of treatment has shown a small improvement in %ITR in the Model phase compared to the Doctor phase (mean difference 0.92%, p = 0.84). A further analysis was performed after excluding the 5 patients with medical issues. The reason for this exclusion was that the medical issues occurred during the Model phase in 4 of these patients as compared to 1 that occurred during the Doctor phase. This, therefore, distorted the results of the time in therapeutic range of the Model phase (Table 13) resulting in biased comparison of the two phases of treatment.

**Table 21. Descriptive statistics and p-values of the effect of genetic and non-genetic variables on daily warfarin dose (mg/kg/day)†**

| Variable | N | Median | Minimum | Maximum | p-value |
|---|---|---|---|---|---|
| **Age groups (years)** | | | | | |
| **1-5** | 10 | 0.2 | 0.1 | 0.4 | 0.17§ |
| **6-10** | 6 | 0.1 | 0.1 | 0.2 | |
| **11-18** | 10 | 0.1 | 0.1 | 0.2 | |
| **Gender** | | | | | |
| **Male** | 18 | 0.2 | 0.1 | 0.4 | 0.11‡ |
| **Female** | 8 | 0.1 | 0.1 | 0.2 | |
| **Ethnicity** | | | | | |
| **White** | 20 | 0.1 | 0.1 | 0.4 | 0.35§ |
| **Asian** | 4 | 0.2 | 0.1 | 0.2 | |
| **Other** | 2 | 0.15 | 0.1 | 0.2 | |
| **Indication** | | | | | |
| **Fontan** | 20 | 0.1 | 0.1 | 0.2 | 0.16‡ |
| **Mechanical valves** | 6 | 0.2 | 0.1 | 0.4 | |
| **Target INR range** | | | | | |
| **1.5-2.5** | 7 | 0.1 | 0.1 | 0.1 | 0.07§ |
| **2.0-3.0** | 12 | 0.1 | 0.1 | 0.2 | |
| **2.5-3.5** | 4 | 0.2 | 0.1 | 0.4 | |
| **Other** | 3 | 0.2 | 0.1 | 0.2 | |
| **CYP2C9 genotype** | | | | | |
| ***1/*1** | 16 | 0.1 | 0.1 | 0.2 | 0.56‡ |
| ***1/x** | 9 | 0.1 | 0.1 | 0.4 | |
| **VKORC1 genotype** | | | | | |
| **G/G** | 12 | 0.2 | 0.1 | 0.4 | 0.01‡ |
| **G/A** | 14 | 0.1 | 0.1 | 0.2 | |

§ Kruskal-Wallis test.
‡ Mann-Whitney test.
† Analysis performed after excluding the outlier in Figure 23.

**Table 22. Descriptive statistics and p-values of the effect of genetic and non-genetic variables on time in therapeutic range (%ITR and %TTR)**

| | %ITR | | | | | %TTR | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **N** | **Mean (SD)** | **Minimum** | **Maximum** | **p-value** | **Median** | **Minimum** | **Maximum** | **p-value** |
| **Age groups (years)** | | | | | | | | | |
| **1-5** | 10 | 58.75(16.13) | 36.4 | 78 | 0.1† | 83.2 | 52.9 | 90.5 | 0.19§ |
| **6-10** | 6 | 72.63(16.51) | 57.7 | 100 | | 84.75 | 75.7 | 100 | |
| **11-18** | 10 | 75.41(18.76) | 43.8 | 100 | | 90.98 | 69.1 | 100 | |
| **Gender** | | | | | | | | | |
| **Male** | 18 | 67.13(18.83) | 36.4 | 100 | 0.62‡ | 86.15 | 52.9 | 100 | 0.94ǂ |
| **Female** | 8 | 71.13(18.07) | 43.8 | 100 | | 86.1 | 69.1 | 100 | |
| **Ethnicity** | | | | | | | | | |
| **White** | 20 | 67.97(19.49) | 36.4 | 100 | 0.98† | 86.15 | 52.9 | 100 | 0.8§ |
| **Asian** | 4 | 68.93 (9.66) | 57.7 | 77.7 | | 87.4 | 77.8 | 95.6 | |
| **Other** | 2 | 71.05(29.77) | 50 | 92.1 | | 88.3 | 82.2 | 94.5 | |
| **Indication** | | | | | | | | | |
| **Fontan** | 20 | 72.30(17.57) | 36.4 | 100 | 0.04‡ | 88.45 | 59.3 | 100 | 0.04ǂ |
| **Valve replacement** | 6 | 55.23(15.44) | 44.1 | 82.3 | | 65.55 | 52.9 | 94 | |
| **Target INR range** | | | | | | | | | |
| **1.5-2.5** | 7 | 79.74(15.52) | 63.4 | 100 | 0.17† | 88.95 | 75.7 | 100 | 0.21§ |
| **2.0-3.0** | 12 | 67.45(17.61) | 36.4 | 94.5 | | 85.75 | 59.3 | 99.8 | |
| **2.5-3.5** | 4 | 55.25(18.25) | 44.1 | 82.3 | | 63.28 | 52.9 | 94 | |
| **Other** | 3 | 62.9 (20.68) | 45.4 | 85.7 | | 77.75 | 61.5 | 97.1 | |
| **CYP2C9 genotype** | | | | | | | | | |
| ***1/*1** | 16 | 72.15(17.25) | 36.4 | 100 | 0.28‡ | 88.45 | 57.0 | 100 | 0.36ǂ |
| ***1/x** | 9 | 63.66(19.92) | 43.8 | 100 | | 80.5 | 52.9 | 100 | |
| **VKORC1 genotype** | | | | | | | | | |
| **G/G** | 12 | 61.50(15.31) | 44.1 | 85.7 | 0.08‡ | 83.25 | 52.9 | 97.1 | 0.11ǂ |
| **G/A** | 14 | 74.23(19.17) | 36.4 | 100 | | 89.4 | 59.3 | 100 | |
| † ANOVA test. ‡ Independent sample t-test. § Kruskal-Wallis test. ǂ Mann-Whitney test. | | | | | | | | | |

The adjusted improvement in %ITR between the Model phase over the Doctor phase comparison made after excluding the 5 cases with medical issues has also shown a non-significant difference between the two phases of treatment (mean difference 5.77%, $p = 0.22$). However, the model-based dosing approach was able to achieve more than 50% of the estimated effect size (11%). It is also worth noting the difference in %ITR obtained from the retrospective data, upon which the effect size and sample size were estimated, and that obtained during the Doctor phase of the prospective study. The retrospective data included children who started their warfarin treatment between the years 2000 and 2014 whereas the prospective study follow up period was between November 2015 and April 2017. The %ITR obtained from the retrospective data was 54.06% whereas that of the Doctor phase was 67.9% and 65.5% after excluding the cases with issues. This difference may explain the non-significant results obtained from comparing the two phases of treatment.

Similarly, the overall comparison of the percentage of time in target range (%TTR) between the Model phase and the Doctor phase has shown a non-significant difference between the two phases of treatment (mean difference 5.27%, $p = 0.09$). However, the %TTR of the Model phase was found to be statistically significantly better than that of the Doctor phase ($p = 0.03$) after excluding the 5 cases with medical issues. The reason behind obtaining non-significant difference in %ITR and significant difference in %TTR may be attributed to the difference between the two approaches in calculating the time in therapeutic range. The %ITR is simply the proportion of INR values within the target range whereas the %TTR allocates an INR value for each day between subsequent INR tests according to the linear interpolation approach (Rosendaal et al., 1993). Although having the advantage of being easy to calculate, the %ITR underestimates the time in

therapeutic range in children, particularly in the periods of instability during which the INR is tested more frequently for dose adjustment. Therefore, the %TTR can provide a better estimation of the time in therapeutic range in this population (BISS et al., 2011). In addition, in this research project there were many times where the INR measurements were very slightly above or below the target range and thus they were considered as out-of-range measurements. This led to an underestimation of the time in therapeutic range calculated as %ITR whereas the %TTR provided a better estimation.

The subgroup analysis of time in therapeutic range has shown that the model-based warfarin dosing has overall improved the time in therapeutic range, though it was not statistically significant for most of the subgroups because of the small sample size (Figure 22). However, the %TTR of the Model phase was statistically significantly higher than that of the Doctor phase for patients with Fontan circulation after excluding the cases with medical issues. It is also important to note that the model-based approach to warfarin dosing did improve the time within therapeutic range for children who were described as being more challenging by the health care professionals (Chapter 6). These included children below 5 years of age (mean difference in %TTR 4.8%, $p = 0.29$), adolescents (mean difference in %TTR 2.3%, $p = 0.58$) and children with mechanical heart valves (mean difference in %TTR 4.1%, $p = 0.51$).

The median frequency of INR measurements per month was slightly higher for the Model phase as compared to the Doctor phase (2.3 vs 1.9 measurements per month). This was also because of the slightly above- or slightly below- range INR measurements. These measurements were strictly considered as out-of-range measurements during the Model phase dosing and hence earlier testing schedules were recommended. In comparison, during the Doctor phase of dosing, such measurements were considered to

be of little clinical significance by clinicians and hence longer testing schedules were recommended. In addition, these results might also have been affected by personal experience in warfarin dosing/monitoring during both the Model and Doctor phases. During the Model phase, the decision relating to the next INR test was made by the researcher and hence it depended on the researcher's personal experience. Thus, the testing intervals tended to be shorter in the early months of study and then longer as more experience was gained during the study period. During the Doctor phase, there was also inter-individual variability in the dosing/monitoring process depending upon the individual doctor's experience in this process. Senior doctors who were more experienced with the dosing/monitoring process tended to recommend longer testing intervals, whereas junior doctors with less experience in the process tended to recommend shorter intervals (Chapter 6).

The median frequency of dose changes was statistically significantly higher for the Model phase as compared with the Doctor phase (6.5 vs 2.5). This was because of the method of dose estimation by the model where it adjusts the dose to the mean of the target range and thus may recommend dose changes for only slight changes in the INR measurements (Chapter 2, Section 2.2). In contrast, such slight changes in the INR values were not considered of clinical significance and hence, no dose changes were recommended during the Doctor phase. The subgroup analysis of the frequency of dose changes has also shown that overall the Model phase has higher number of dose changes than the Doctor phase. This difference was higher for the target INR range of 2.0-3.0. However, this subgroup included three patients with medical issues whose periods of more frequent dose changes during the Model phase may have affected the result.

The model-based warfarin dosing resulted in lower levels of over-anticoagulation shown as lower numbers of INR values ≥ 4.0 and ≥ 5.0, though this was not statistically significant. However, most of the minor bleeding complications reported on the received symptom diary cards occurred during the Model phase. Yet, these events occurred during periods where the INR measurements were within the target therapeutic range. Besides, only 8 out of 26 cards were received back from the families, thus it was not possible to estimate which phase of treatment had the greater number of minor bleeding events.

As described earlier in Chapter 4, Section 4.4, the local practice at the EMCHC is to keep the patients within an acceptable INR range with the concern being more about how far the INR measurements were above or below the target range that may predispose to the risk of bleeding or thrombosis, respectively. This will be discussed in detail in Chapter 6. Warfarin treatment was withheld on 2 occasions during the Model phase. In contrast, the treatment was withheld on 3 occasions during the Doctor phase and vitamin K was used in one of these occasions. Alternatively, IV heparin was used in on 6 occasions during the Model phase as compared to 4 occasions during the Doctor phase. This may imply that model-based warfarin dosing can improve the anticoagulation control of warfarin particularly that regarding reducing the incidence of having very high INR values that can predispose to bleeding events.

Genotype-guided and PK/PD model-based dosing of warfarin in adults has been shown to significantly increase the time in therapeutic range (Pirmohamed et al., 2013; Perlstein et al., 2012) and decrease the incidence of over-anticoagulation (Pirmohamed et al., 2013). However, these studies were conducted during initiation of warfarin treatment, hence comparison with the findings in this study was not possible.

Age and weight were found to be significantly correlated with the average daily warfarin dose. This is consistent with the results obtained from studies conducted in children that have also found significant correlations between these demographic variables and warfarin dose (Biss et al., 2012; Moreau et al., 2012; Shaw et al., 2014; Wakamiya et al., 2016). Patients in the youngest age range (1-5 years) were found to require higher weight-adjusted warfarin doses than those in the older age groups, though this was not statistically significant. Results from the largest cohort study of children on warfarin treatment have shown that children between 1 and 6 years of age required significantly higher weight-adjusted warfarin maintenance doses compared to those in the older age groups (Streif et al., 1999). In another study, similar findings were observed in children aged 1-11 years compared to those aged 12-18 years. This was attributed in part to the developmental changes in the weight-adjusted clearance of S-warfarin that was also found to be significantly higher in the younger age group. In contrast, the same study found non-significant differences in the liver weight-adjusted clearance of S-warfarin and the liver weight-adjusted dose of warfarin (Takahashi et al., 2000). This can be explained by the non-linear relationship that exists between drug clearance and body weight (B. J. Anderson and Holford, 2008).

There was a non-significant difference in warfarin dose requirements between patients with the wild type CYP2C9 and those with the variant alleles. This may be due to the small number of the genotype subgroups. In addition, the study sample did not involve any patients with homozygous variant alleles that require the lowest warfarin dose requirements. CYP2C9 genotypes were found to significantly affect warfarin dose requirement in children in some studies (Biss et al., 2012; Vear et al., 2014) whereas others did not find a significant effect (Moreau et al., 2012; Nguyen et al., 2013; Nowak-

Göttl et al., 2010). Conversely, patients in this study with the wild type VKORC1 were found to have statistically significantly higher warfarin doses than those with the heterozygous variant allele. Similar findings were obtained from previous studies conducted in children (Biss et al., 2012; Moreau et al., 2012; Nguyen et al., 2013; Vear et al., 2014; Wakamiya et al., 2016), however, other studies found non-significant difference in warfarin dose requirements between children with the wild type VKORC1 and those with the heterozygous variant allele (Nowak-Göttl et al., 2010; Shaw et al., 2014). It is also important to note that the study sample did not involve patients with homozygous VKORC1 variant allele, therefore it was not possible to assess its effect on warfarin dose requirement.

Despite being non-significantly different, patients with Fontan circulation tended to receive lower warfarin doses than those with mechanical heart valves. This may be due to the lower target INR ranges used for patients with Fontan circulation due to the lower levels of anticoagulation required or due to the presence of an underlying abnormality in liver function (Whiteside et al., 2016; Kaulitz et al., 1997). Warfarin dose requirement was found to be significantly lower in patients with Fontan circulation as compared to other indications in some studies (Biss et al., 2012; Shaw et al., 2014), whereas other studies found non-significant difference (Nguyen et al., 2013; Wakamiya et al., 2016).

Interestingly, there was one patient who required very high average warfarin maintenance dose (about 18 mg/day). This may be attributed to warfarin resistance due to rare mutations in VKORC1. However, malabsorption, poor adherence and PK interactions need to be excluded and serum warfarin concentration measured to confirm the likelihood of warfarin resistance (Rost et al., 2004; HARRINGTON et al., 2008).

The effect of genetic and non-genetic factors on the time in therapeutic range was also evaluated. Patients in the lowest age range (1-5 years) tended to have lower time in therapeutic range than the other age groups, though the difference was not statistically significant. The largest cohort study in children has shown that children aged between 1 and 6 years had significantly lower percentage of INR values in the target range than older patients (Streif et al., 1999). This can be attributed to several factors. The maturation of the coagulation system approaches near-adult levels by 6 months of age. However, the levels of the coagulant and anticoagulant proteins are still 20% lower than the adult values until late teenage years (Monagle et al., 2006) which can cause variable response to warfarin. Besides, children in this age group are more susceptible to inter-current illnesses such as infections, diarrhoea and vomiting which may require the use of antibiotics and this may affect the absorption and metabolism of warfarin and hence the response to the it (Monagle, Newall and Campbell, 2010). These findings were also demonstrated in the accounts obtained from the doctors and nurses at the EMCHC (Chapter 6) who confirmed that warfarin treatment control was challenging in this age group.

Patients with Fontan circulation had significantly higher time in the therapeutic range than those with mechanical heart valves. Streif *et al*. (1999) study found non-significant difference in the percentage of in-range INR values between children grouped into Fontan, congenital heart disease (CHD) and non-CHD indications (Streif et al., 1999). In contrast, in a different study, children anticoagulated for mechanical mitral valves were found to spend significantly lower time within the target therapeutic range than those anticoagulated for Fontan circulation and mechanical aortic valves (Bhat et al., 2010). Besides, mechanical mitral valve replacement was found to be the only factor associated with poor anticoagulation control (Bhat et al., 2010). Moreover, other study results have

shown that children with mechanical heart valves had the lowest time in the therapeutic range compared to other indications for warfarin in the cohort studied (Jones et al., 2016). Furthermore, in a study of a cohort of 25 children with mechanical heart valves, only 44% of the INR observations were within the target therapeutic range (Wong et al., 2011). However, none of these studies has identified factors associated with the low time in therapeutic range observed in children with mechanical heart valves. Interestingly, the doctors and nurses at the EMCHC thought that the frequent INR monitoring and dose changes in children with mechanical valves was the cause of the fluctuating INR control in this population. This will be discussed in detail in Chapter 6.

Patients with the wild type CYP2C9 showed a tendency to have higher time in the target therapeutic range. This is consistent with a previous study results which showed that children with heterozygous variant alleles of CYP2C9 had higher frequency of above-range INR values than those with the wild type allele (Ruud et al., 2008). In contrast, patients who were heterozygous for the variant VKORC1 allele showed a tendency to spend longer time in the therapeutic range. In a study conducted in children during the first 6 months of warfarin treatment, VKORC1 variant allele was also shown to be associated with greater time in the therapeutic range in children in the first 6 months of warfarin treatment (Hawcutt et al., 2014).

A limitation in this research project was the small sample size. However, this work was designed to be a pilot study to assess the model-based warfarin dosing in clinical practice and the sample size was estimated accordingly. The cross-over design was selected to minimise the likelihood of inter-individual variability in warfarin dose/response. The cross-over design was also chosen in order to reduce the sample size required to obtain a statistically significant difference as a parallel design would require larger sample sizes

that would be more difficult to recruit and manage within the limited time and resources available for the study. Another limitation of the study was that there was no wash-out period upon crossover from one phase to another and also upon randomisation to the Model phase. This may have affected the results of time in the therapeutic range when the INR on crossover/randomisation was out-of-range. However, the wash-out period was not feasible in this study as children required constant anticoagulation with warfarin to prevent TE events and withholding warfarin treatment could predispose children to serious events that might be life-threatening.

This study has also involved challenges in the recruitment and follow up periods. The recruitment process was difficult and time-consuming. Families had to be first approached by the cardiac liaison nurse during the regular phone calls to report the INR values or the hospital follow up visits. This was time-consuming taking into account the usual daily workload of the nurse. In addition, the consenting process was done through the post and was also very time-consuming. Posting the participant information sheets to families, making the phone calls to discuss the study details with the parents and getting the signed consent/assent forms back from the families were very-time consuming. Moreover, the recruitment process was difficult where there was a total of 48 families screened from whom only 29 families consented to participate in the study. Some families provided reasons for their declined consenting whereas others did not. The reasons provided by the families included either family circumstances, change in the child's medical condition which made the parents no longer willing to participate or the parents' concerns about their child's involvement in the study despite reassurance that the model-derived doses would be reviewed by the doctors before being prescribed to their children. Furthermore, there was a significant number of families who did not respond to the phone

calls made by the researcher. Some of these families sent signed consent/assent forms whereas others did not, the thing that was also difficult and time-consuming during the recruitment process.

Besides, the follow up period was very challenging. Parents of children on long term warfarin treatment could ring or come to the hospital anytime during the day to report the INR test result or perform the INR test, respectively. Their warfarin dose could subsequently be reviewed and adjusted by any of the doctors available in the hospital. For children in the Model phase of treatment, this was challenging to the researcher as this could happen anytime during or out of the workday hours, for example very late in the evening or during weekends and bank holidays. The researcher had to chase the INR test results for the patients, and especially those who did not ring during the workday hours in order not to be mistakenly dosed by the doctors. However, dosing was missed on some occasions where the doctors/nurses did not recognise that those patients were on the Model phase of the study. The challenge of chasing the INR test results and dosing outside the workday hours involved inpatients too. Hospital admissions could be at Glenfield hospital, other hospitals in Leicester, or in hospitals that are outside Leicester. Despite being also dosed at the EMCHC, warfarin dosing was also missed on some occasions for the inpatients. In addition, there was the issue of some families who did not ring or come to hospital to test the INR on the prescheduled times and some others who used to ring only when the INR is outside the target range which has affected the study results.

Despite all limitations and challenges, this research project in children on long-term warfarin treatment has shown that model-based warfarin treatment can improve the time in therapeutic range, particularly for children with Fontan circulation, and reduce over-anticoagulation. Although the aimed 11% effect size was not achieved in the overall

results of %ITR and %TTR, it was obtained in the results of %TTR after excluding the 5 cases with medical issues. However, model-based warfarin dosing was associated with a higher frequency of dose alterations. Further studies with larger sample size are required to assess the model-based warfarin dosing in children. A sample size that includes a greater number of children with mechanical heart valves and more children with variant alleles of CYP2C9 and VKORC1 would provide a more conclusive evaluation of the model-based warfarin dosing. This would also provide a better understanding of the effects of genetic and non-genetic factors on warfarin dose requirement and time in therapeutic range in children on long-term warfarin treatment.

# ***Chapter Six***

# *The qualitative study*

# Chapter 6: The qualitative study: Exploration of the experience of patients/parents and health care professionals of warfarin treatment and the new dosing approach

## 6.1. Introduction

The maintenance of optimal warfarin therapy involves not only adherence to the prescribed regimen, but also careful attention to diet and medicines that may interact with warfarin, restriction of alcohol intake and being cautious about physical activities that can predispose to injuries and bleeding. It will therefore be appreciated that there is a multitude of factors that can add a significant burden both on the child and the parents. Therefore, it is pivotal to explore the lived-experience of being involved in warfarin dosing and monitoring to gain an in-depth understanding of how patients/parents handle the day-to-day warfarin treatment. Lived-experience means understanding the perceptions, beliefs and attitudes of managing warfarin treatment through the eyes of the patients and parents to enhance warfarin control in this population.

Individualising warfarin dosing by taking into account the factors that affect its PK and PD is pivotal. However, the application of the new dosing approach in clinical practice requires not only the results of the clinical trial that indicate its clinical effectiveness but also the acceptance of both the health care professionals and the patients/parents. Therefore, it is important to also explore the experience of the doctors and nurses involved in warfarin dosing and monitoring as well as that of the patients/parents with the new dosing approach. In addition, it is essential to obtain an in-depth understanding of how warfarin dosing and monitoring is performed in usual clinical practice to improve the performance of the new dosing approach to be suitable for daily clinical care. Therefore,

it is pivotal to explore the lived-experience of the doctors and nurses with managing warfarin treatment.

This research project involves exploring the views and perspectives of patients/parents and health care providers about the long-term management of warfarin treatment in addition to their views of the new warfarin dosing approach.

### 6.2. Methodology

See Chapter 2 Section 2.5

### 6.3. Results

Eleven interviews were conducted and transcribed verbatim (Appendix 7). In order to retain the participants' confidentiality, pseudonyms have been used (Table 23).

**Table 23. Pseudonyms and descriptions of the study participants.**

| | |
|---|---|
| John | A 17-years old patient (Group 2) |
| Grace | Mother of John |
| Michelle and Evan | Parents of a 2-years old patient (Group 2) |
| Sonya | Mother of a 3-year old patient (Group 1) |
| Kamya | Mother of an 8-year old patient (Group 1) |
| Sarah | Consultant paediatric cardiologist |
| George | Paediatric cardiology registrar |
| Taj | Paediatric cardiology registrar |
| Shirley | Cardiac liaison nurse |
| Madison | Cardiac liaison nurse |

### 6.3.1. Doctors' experience with managing warfarin therapy post cardiac surgery

Analysis of the doctors' interviews led to the emergence of three major thematic areas; the medical and clinical knowledge, the INR monitoring and the dose decision.

#### 6.3.1.1. The medical and clinical knowledge

The medical and clinical knowledge of the doctors was perceived to play a central role in the process of managing warfarin treatment in children. Management of warfarin treatment involved establishing the target INR range, initial warfarin dosing, overlap with heparin, INR monitoring and subsequent dose adjustments. The doctors agreed that the key determinants of managing warfarin treatment in children with congenital heart disease were the indication for warfarin use and the patient's clinical condition. At the EMCHC, the indications for warfarin use after congenital heart surgery were Fontan procedure, mitral valve replacement (MVR) and aortic valve replacement (AVR).

> 'It is depend on the underlying diagnosis… and the difficulties during surgery and the size of the patient and… the artificial valve... and the cardiac function'
> (Dr. Sarah, Interview 4, Lines 2796-2798)

> 'Oh, when so that's pretty much depends on the indication and on the patient's condition'
> (Dr. George, Interview 3, Lines 2409-2410)

The doctors agreed that different target INR ranges were used for the different indications of warfarin use. There was also variability in the target INR ranges for the same indication and this was dependent on the clinical condition of the patient and the consultant's preference. Higher target INR ranges were used for patients with mechanical heart valves than those with Fontan procedure because of the perceived higher risk of thrombosis associated with the mechanical valves. According to the doctors, patients with MVR were even at more risk of thrombosis than those with AVR. Taj explained that the blood flow through the mitral valve is slower than that through the aortic valve and hence

there is more risk of thrombosis on the mechanical mitral valves than on the mechanical aortic valves. The target INR ranges could be tailored according to the patients' clinical condition where lower target ranges were used when there was a risk of bleeding or conversely higher targets were used for patients with small heart valves. In addition, the target INR range could be transiently changed if there was an acute change in the patient's clinical condition. Once the acute condition had resolved, the original target range was reused.

> '… we have had patients who have had internal cranial bleeds and things like that we have… targeted lower INRs, other patients who have had narrow prosthetic valves who we have targeted slightly higher INRs and so it's not a one size fits all'
> (Dr. George, Interview 3, Lines 2447-2450)

> **'**Sometimes yes change the target temporary because there is an acute change in the situation then when it resolves you go back to your previous target' (Dr. Sarah, Interview 4, Lines 2966-2967)

The doctors maintained that warfarin treatment was initiated at a relatively standard loading dose of 200 µg/kg. This loading dose might be repeated on the following day if the INR value was still low. Afterwards, the warfarin dose was adjusted according to the INR level.

> 'OK that tends to [be] a fairly standard initial dose of warfarin that we use within 200 micrograms per kilo up to a maximum of about 10 milligrams for an initial loading dose then we re-check the level the following day, if the level is still low then we'd repeat that and then if it's at a reasonable level that point we'd half that dose of 200 micrograms per kilo'
>
> (Dr. George, Interview 3, Lines 2401-2406)

The overlapping time of warfarin with heparin was also variable and depending on the indication for anticoagulation. Because of the perceived higher risk of thrombosis, adequate anticoagulation was required for patients with mechanical valves. Therefore,

these patients were required to achieve therapeutic levels of heparin and hence longer time of overlap with warfarin than those with Fontan procedure.

Monitoring warfarin treatment through INR testing and subsequent dose adjustments was also dependent on the indication for anticoagulation and the patient's clinical condition. The doctors agreed that they were more cautious with patients with mechanical valves, particularly those with MVR, than those with Fontan procedure. The reason behind this, according to the doctors, was the perceived higher risk of thrombosis in patients with MVR, therefore, these patients were tested more frequently.

> '… for example we are more lenient with the Fontans because there is no immediate risk if they drop significantly on the conduit but with valve especially mitral valve we become very anxious if there is.. a significant change in the INR.. so we tend to test the valves more frequently and less frequently for the Fontans'
>
> (Dr. Sarah, Interview 4, Lines 2881-2885)

The doctors believed that dose adjustments made for out-of-range INR values were also variable and dependant on the indication and how far the INR values were out of range. The doctors expressed their concerns about INR values that were on the lower side of the target range and those which were below the target range in patients with MVR because of the associated risk of thrombosis. The general approach adopted by the doctors was to keep slightly high INR values to avoid the risk of under-anticoagulation that would require hospital admission for intravenous heparin treatment. The doctors were also very cautious about stopping warfarin treatment with very high INR values in patients with MVR because of fears of severe drop in the INR level and subsequent risk of thrombosis. It is important to note that the doctors were more concerned about thrombotic events than about bleeding events when monitoring warfarin treatment in patients with MVR. Conversely, both below-range and above-range INR values in patients with Fontan

procedure were of less concern to the doctors because of the perceived lower risk of thrombosis and bleeding, respectively.

> 'Patients, for example with mechanical mitral valve, I tend to be very cautious about reducing the dose too rapidly and.. I'll err on the side you keep the INR slightly high as long as there is no evidence of active bleeding… stop the warfarin at that dose, we often find that we get a rebound drop then that will need to be admitted for intravenous heparin treatment because he can't have a lower INR with the mechanical mitral valve'.
>
> (Dr. George, Interview 3, Lines 2500-2510)
>
> Taj: … Fontan group... because you are not worried of bleeding even after 6... in practice I haven't seen patient who bled, so you are not worried, yes you want to maintain them somewhere between 1.5 to 4 but even 5 and 6 and 7, we haven't seen many bleeding in practice'
>
> Interviewer: OK so you so you do concern about those.. with low INRs greater than those with high [INRs]?
>
> Taj: Yeah especially with the mechanical valve because there is element of clotting. In Fontan group even their INR is low, we can still build up in next few days so we are not worried.. if they have a transient few days of low INR.
>
> (Dr. Taj, Interview 7, Lines 3340-3355)

Treatment of the slightly out-of-range INR values was also dependant on the indication of warfarin use. The doctors were less concerned about patients with Fontan procedure who had slightly above- or below-range INR values. However, more concerns were expressed about patients with mechanical heart valves who had slightly below-range INR values, and once again, because of fears of risk of thrombosis. George also thought that these slightly out-of-range INR values could be attributed to the possibility of errors in the home INR testing machines.

> '… If you've got a patient who has a Fontan circuit who's on anticoagulation, it's not a 100% critical where the INR is 2 as a long-term persisting 1.9 or 1.8. If you have a patient with mechanical valve in and their INR is very slightly high you got a target of 3 to 4 and it's 4.1, again I'm not worried about that so much. If you have patient his INR erring on the low side [and]

> he's got mechanical valve then yes I would do something about that, so it's very much take the clinical picture in'
>
> (Dr. George, Interview 3, Lines 2531-2540)

Personal experience in prescribing warfarin was perceived to be very important in dose decision in response to changes in the INR values. The doctors felt that there was variability in prescribing warfarin doses between different doctors where some doctors tended to over-treat the slightly out-of-range INR values.

> '… even there is some.. interpersonal variation among the doctors. The dose which I'm going to prescribe not necessarily exactly the same dose would be prescribed by my other colleague'
>
> (Dr. Taj, Interview 7, Lines 3429-3431)
>
> 'I also think sometimes… some of the doctors over-treat the slightly high slightly low results and tend to not have the idea of what's happening with trying to smooth everything out'
>
> (Dr. George, Interview 3, Lines 2756-2758)

In their accounts about the obstacles encountered in maintaining therapeutic INR levels, the doctors agreed that INR control was very difficult in young children, particularly those under one year of age. George explained that children in this age group were more susceptible to infections and illnesses like diarrhoea and vomiting which could affect warfarin absorption. Besides, the more frequent antibiotics' use in this age group could interfere with the liver metabolism of warfarin. Moreover, the use of formula milk that contains vitamin K in this age group could counteract warfarin action. Furthermore, the accuracy of dosing of the liquid dosage form of warfarin was questioned, particularly that relating to adequate shaking of the bottles prior to administration and the variability that might be encountered when administering doses that can be as small as 0.2 ml or 0.3 ml.

The INR control was also difficult in adolescent patients, particularly those with mechanical valves. The doctors questioned the adherence of adolescent patients to warfarin treatment and pointed out the issue of alcohol intake in this age group that could affect the anticoagulation control of warfarin.

> 'The younger children, they can even have quite labile warfarin control particularly patients under the age of one, they are very very difficult…'
>
> (Dr. George, Interview 3, Lines 2606-2607)
>
> 'There are few.. adolescent patient with the mechanical valves who we sometimes question their dosing and they have.. recreation thing or alcohol and all these things, so that sometimes interfere with the controlling of their INR within range and few of them would even miss warfarin..'
>
> (Dr. Taj, Interview 7, Lines 3163-3167)

According to the doctors, guidelines for warfarin dosing and INR monitoring were available, however, they were individualised according to the clinical conditions of the individual patients.

> **'**There are guidelines but they can be individualised to a certain degree to various circumstances'
>
> (Dr. George, Interview 3, Lines 2453-2456)

#### 6.3.1.2. The INR monitoring

As described earlier, the key determinants of the process of monitoring the INR level were the indication for warfarin use and the patient's clinical condition. As said by the doctors, the use of different target INR ranges for the different indications of warfarin was based on the differences in the risk of thrombosis between the different indications. Patients with mechanical heart valves were perceived to have higher risk of thrombosis than those with Fontan procedure. Besides, patients with MVR were perceived to be at higher risk of thrombosis than those with AVR because, as explained by the doctors, of

the slower blood flow through the mitral valve that can increase the risk of thrombus formation. Therefore, higher target INR ranges were used for patients with MVR and lower target ranges were used for patients with AVR and Fontan procedure.

> '… patients with the extra-cardiac Fontan conduits.. tend to have a target INR of 2 to 3, patients with mechanical mitral valves tend to have a range between 3 and 4, patients with mechanical aortic valves tend to have a range between 2.5 and 3.5'
>
> (Dr. George, Interview 3, Lines 2440-2443)

The target INR ranges could be individualised according to the clinical condition of the patient. For example, lower target ranges were used when there was a risk of bleeding or conversely, the use of higher target ranges in patients with very small valves. In addition, the target INR ranges could be temporarily changed when there was an acute change in the clinical condition of the patient. The original target range was reused when the clinical condition had resolved (Section 6.3.1.1).

The process of INR monitoring was also dependant on the indication for warfarin anticoagulation and the patient's clinical condition. The doctors expressed more concerns about patients with mechanical heart valves, particularly those with MVR, than patients with Fontan procedure because of the perceived higher risk of thrombosis. Therefore, when monitoring the INR of patients with Fontan procedure, the doctors accepted a wide range of INR values above and below the target range. Besides, INR values that were slightly above or below the target range were not worrying to the doctors who attributed this to the possibility of errors in the home INR monitoring machines. In contrast, in patients with mechanical valves, particularly those with MVR, INR values that were on the lower side of the target range or those that were below the target range were very concerning to the doctors (Section 6.3.1.1). Therefore, the doctors were monitoring the INR of these patients more frequently to avoid any possibility of having low INR values.

> ‘And in Fontan group, you are relax because you know higher won’t give them bleeding… So there is much big room for them even [if] they fluctuate and even [if] they go lower [than] 1.5 or low still it’s not much that risk of clotting because there isn’t any mechanical valve’
>
> (Dr. Taj, Interview 7, Lines 3371-3380)
>
> ‘For mitral valve we do very frequent INR monitoring and simple reason being there is more risk [of clotting] so we want to avoid any sort of low INR situation hidden…’
>
> (Dr. Taj, Interview 7, Lines 3131-3133)

The doctors explained that patients with mechanical valves, particularly those with MVR, and having very low INR values needed to be admitted to the hospital to receive intravenous heparin treatment. This could be inconvenient for the patients because of the hospital admission itself and the need for intravenous access for frequent blood testing and receiving treatment. The most worrying group to the doctors were infants with small mechanical mitral valves because of the associated high risk of the valve not functioning well. Therefore, the doctors preferred to keep slightly high INR values when monitoring patients with mechanical heart valves.

> ‘… most of the consultants would admit that patient [with MVR] to start an intravenous heparin if the INR goes below 2, particularly in smaller patients so, mechanical mitral valves in infants are very very high risk group..….. So to aid avoid the risk of having this thrombosis, I think it’s more dangerous to have a slightly low INR than to have a slightly higher INR. So therefore, when I’m dosing them I keep that in mind and I tend to err on the side of keeping it slightly high.’
>
> (Dr. George, Interview 3, Lines 2564-2580)

More frequent INR testing was also required during the periods of intercurrent illness, infections and antibiotics’ use as this could cause a disturbance in the INR control of the patients. In contrast, the doctors indicated that patients with Fontan procedure required less frequent INR testing because of the perceived lower risk of thrombosis and the wide range of INR accepted.

> ‘For a Fontan.. since we have a big range acceptable range from low to [high], so we monitor three weekly or four weekly.… although in practice we had to do relatively sooner because of this population.. where you have some unseen things like diet and for kids.. intercurrent illness, sometimes they are on antibiotic or even infection so that determines their.. intermittent change in the follow up or frequency of INR checking’
>
> (Dr. Taj, Interview 7, Lines 3138-3151)

The doctors tried to make the time interval between the INR measurements as long as possible. After making a dose change, a minimum interval of three days was recommended before re-checking the INR level. However, it was sometimes recommended to perform the INR sooner to have an idea about the rate of change of the INR to help in deciding the next dose of warfarin.

> ‘I try to extend the interval to as long as I can because I think if you measure a transitional INR, it’s OK as long as you realise that it’s a transitional INR.. you don’t react to it too much. And I think sometimes it’s useful to do short term INRs to see.. [the] rate of change so you can.. see where things are likely to head and if your rate of change is too high then it might make you come up a little bit on the next dose, but I usually if I do a dose change I’ll usually try and leave it at least 3 days before rechecking’
> (Dr. George, Interview 3, Lines 2683-2690)

When the doctors were asked about the obstacles that they faced in maintaining the INR in the target therapeutic range, they agreed that the INR control was most difficult in two age groups; the young children and the adolescents. Children below 5 years of age were more prone to frequent intercurrent illnesses like diarrhoea and vomiting which could interfere with warfarin absorption and subsequently the INR control. In addition, young children were more susceptible to infections and antibiotics’ use which could affect warfarin metabolism and hence the INR control. Moreover, using formula milk which contains vitamin K in infants less than 1 year of age was also a contributing factor to the INR instability in this age group. Furthermore, the accuracy of the dose administered was doubted even when the liquid dosage form of warfarin was used. The other age group

where the INR was difficult to control was the adolescent patients. The adherence of adolescent patients to taking the medication or taking the prescribed dose of warfarin was questioned, besides, the use of alcohol in this age group was also a contributing factor to the INR instability (Section 6.3.1.1.).

> ‘And we’ve also had some patients.. particularly teenagers.. where compliance with taking the medication, we can never know for sure, but we think that has been an issue in those patients as well.. you sometimes get these patients who you think probably don’t take as much as that been prescribed or don’t take it at all or miss some doses then their INR control tend to be extremely difficult’
>
> (Dr. George, Interview 3, Lines 2628-2634)

As described earlier in Section 6.3.1.1, guidelines for the INR monitoring were available, however, they were customised according to the clinical conditions of the individual patients.

#### 6.3.1.3. Warfarin dose decision

Warfarin dose adjustments were usually made when the INR was out-of-range. Once again, the indication for warfarin use and the patient’s clinical condition were the key determinants of the dose decision. When deciding warfarin dose, the doctors expressed more caution with patients with mechanical heart valves, especially those with MVR, than those with Fontan procedure. The reason, as described earlier, was the perceived higher risk of thrombosis in patients with mechanical valves. Besides, the dose decision was also dependant on how far the INR values were out-of-range and the rate of change of INR. As described earlier, slightly out-of-range INR values in patients with Fontan procedure were not worrying to the doctors. However, INR values that were on the lower side of the target range and those which were below the target range in patients with mechanical valves were very concerning to the doctors because of the associated risk of thrombosis. Therefore, the doctors favoured keeping relatively high INR values when

deciding warfarin doses to avoid the risk of under-anticoagulation that might require hospital admissions for intravenous heparin. In addition, the doctors were less concerned about the bleeding events associated with very high INR values. Therefore, they were very cautious about reducing or stopping warfarin treatment when the INR values were very high because of fears of having rapid INR drop to very low levels that might predispose to thrombus formation (Section 6.3.1.1).

The doctors felt that dose decision was challenging in a group of patients in whom very small dose changes were associated with significant changes in the INR values. Another challenging group was the very young children with small mechanical valves in whom the dose adjustments were very small. Therefore, the doctors were even more cautious in deciding warfarin doses in such patients.

> 'It is true that there are a few patients… [who] have a greater response [to] little change in the dose so if you increase dose slightly because of their low reading you find it going very high so they have a very narrow.. dosing range'
>
> (Dr. Taj, Interview 7, Lines 3263-3266)
>
> 'There's also the group that have the hardest warfarin control as well because the dose change per body weight is such a fine thing even when you use the solutions that even a change of 0.2, 0.3 of a milligram can be very difficult and also administering that small dose makes the error can be mess, so they do tend to be patients with a higher risk as they've got a much rather a small valve and a small heart and they've got labile INRs anyway'
>
> (Dr. George, Interview 3, Lines 2572-2579)

The doctors' experience in prescribing warfarin was perceived to be essential in dose decision in response to INR changes. There was variability in prescribing warfarin doses between different doctors particularly when the INR values were slightly out-of-range, as described in the doctors' accounts in Section 6.3.1.1.

Guidelines for warfarin dosing were available, however, they were individualised according to the patient's clinical condition (Section 6.3.1.1).

### 6.3.2. Nurses' experience with managing warfarin therapy post cardiac surgery

Four main thematic areas emerged from the analysis of the nurses' interviews. These were the role of the cardiac liaison nurses (CLN) in managing warfarin treatment, adherence to warfarin treatment, the INR monitoring and the dose decision.

#### 6.3.2.1. The role of the cardiac liaison nurses in managing warfarin treatment

At the beginning of warfarin treatment, the CLN role was first to educate the families on the drug itself, including its action, adverse events and interactions. According to the nurses' accounts, practical ways were used in the teaching process for better understanding by the families and written information was provided. The education process also involved training on the home INR monitoring machines for the families who wished to monitor the INR at home.

> '… practical things like vitamin K is found in for example green vegetables and teaching them simply that warfarin is used to thin the blood and there are certain food stuffs that contain vitamin K and vitamin K clots your blood… if you like broccoli, decide how much you gonna have, is it gonna be half a cupful or is it gonna be a cupful and stick to it…. and if you're going to have a pint of beer, you can always have a pint of beer, what you can't do.. is going to have a binge that down the pub at the weekend because that too will interfere with your warfarin levels.'
>
> (Nurse Madison, Interview 6, Lines 4133-4157)

Nurse Madison felt that families needed time to take all the provided information into consideration because of the nature of the medical condition that required frequent hospital visits and admissions. She thought that education was a constant process that needed to be repeated regularly to enhance the families' monitoring of warfarin treatment.

> ‘I find that it takes a while for that to register. I think because they have lots of the other things that they need to take on board with coming to clinics and why they’re coming and you know being stressed out because they might need to be admitted for a procedure..’
>
> (Nurse Madison, Interview 6, Lines 4162-4167)
>
> ‘.. and even now parents who‘ve been using the INR machines for a few years when they come in every 6 months to have their comparison check and you watch them prick the finger and the way they putting the blood on the strip, you thinking to yourself that’s not how I told you how to do it. So you have to re-go back and say actually no, don’t keep doing that….’
>
> (Nurse Madison, Interview 6, Lines 4404-4409)

During monitoring warfarin treatment, the CLN role was to receive the answer phone messages from the families, transfer the information provided through these messages into the individual patients’ INR charts, transfer these charts to the doctors to prescribe warfarin dose and the next INR testing schedule and finally to ring the families back to provide them with the prescribed regimen. Nurse Madison felt that this process was mostly uncomplicated, however, she expressed her fears when it was occasionally unsuccessful to contact the families to provide them with the prescribed warfarin dose and the INR testing schedule.

> Interviewer: so is that process always straight forward?
>
> Madison: nine times out of ten. It only becomes as issue when you’re trying to call a parent back and they’re not answering their mobile or the mobile number says this phone is not available and then you’re in panic station thinking how am I going to get hold of these parents to tell them how much warfarin to give their child and when they’re going to retest and am I going to be able to get hold of them today.
>
> (Nurse Madison, Interview 6, Lines 4103-4109)

The nurses expressed the need for an anticoagulation service. This was attributed to the high volume of phone calls received daily from the families for warfarin monitoring which was time consuming. In addition, the nurses felt that the education process was

time consuming as well as being a constant ongoing process to improve the families' management of warfarin treatment. Moreover, the nurses felt that having a dedicated anticoagulation nurse would enable better communication with the families. From the nurses' perspective, this would enable obtaining better information about the patients' conditions which would improve the dosing/monitoring process and also would give more time to answer any queries about warfarin treatment.

> 'The problem is that the message is left on the answer phone, so.. we can only do our best to tell parents if it's out of range can you tell us are they on antibiotics, have they had a growth spurt, are they generally unwell…. you need to test their INR, you need to ring on the answer phone and you need to tell us…. sometimes you'd like to have a dialogue but you know with the work load in the day… I think we need full time anticoagulation nurse who's going to be there all the time to constant education, a parents have queries whatever, so they can call you up and you can address the issue' (Nurse Madison, Interview 6, Lines 4385-4424)

#### 6.3.2.2. The INR monitoring

The nurses felt that home INR monitoring was more convenient for families. Shirley explained that it saved the time of travelling and minimised the time taken off school and work for patients and parents respectively. Besides, it provided more flexibility to the families during holiday times as well as these periods when patients required more frequent INR testing which might be outside the working days. However, there were a few families where the nurses felt that hospital monitoring was more convenient for them.

> 'I think there is only a couple of patients who've actually preferred to come to the hospital and get checked. And I know a girl who lives down the road from here actually and she is a teenager and the family could have had an INR machine when she was a child, but she never wanted one… She just doesn't want to do it, she just wants to come here and have it done… it's more convenient for her to come here and have it done she doesn't want one'
> (Nurse Madison, Interview 6, Lines 4268-4281)

Regarding the day-to-day monitoring of warfarin treatment, the nurses felt that the doctors were more cautious with patients with mechanical heart valves, particularly those with MVR, than patients with Fontan procedure. This was because of the perceived higher risk of thrombosis in patients with mechanical valves and its devastating consequences. In contrast, the nurses described patients with Fontan procedure as being stable and therefore, they were tested less frequently. However, these patients were also thought to have periods of INR fluctuations when they had growth spurt or had missed warfarin doses.

> '… well certainly [doctors] are more cautious with the valve patients than they are.. with the Fontan circulation… and if their levels are lower then it's not as a disastrous the fact as it would be if you got a mitral valve in place and their INR is low which obviously could be disastrous and the valve could block off so that's why they're more cautious with them'
>
> (Nurse Shirley, Interview 5, Lines 3772-3780)
>
> 'For me, I find that nine times out of ten Fontan patients are quite stable… Obviously there are occasions.. if they've had a growth spurt or some parents have admitted that they've forgotten to give warfarin and that does actually have a massive impact that sometimes it can take about a week or two before they get back to being stable'
>
> (Nurse Madison, Interview 6, Lines 4174-4180)

From the nurses' perspective, the doctors' experience played an important role in deciding the frequency of INR testing where less experienced doctors tended to recommend shorter testing interval than the more experienced ones.

> '… so again it depends how much experience they have had of prescribing warfarin and they're sometimes probably a little bit more cautious would maybe say check more sooner than some of the more senior doctors'
>
> (Nurse Shirley, Interview 5, Lines 3786-3789)

When asked about the causes of the fluctuating INR control in children, Shirley thought that more frequent INR monitoring and dose changes could lead to such changes in the INR control. Besides, she thought that infections and antibiotics' use could have a considerable impact on the INR control. Moreover, growth spurts in children, missed warfarin doses, diet, alcohol use by adolescent patients and use of warfarin in young children were all perceived as causes of unstable INR control in children.

> 'And again it seems sometimes just tweaking little doses or do not realising that actually it'll take a couple of days to you actually see that effect so giving the medication, checking the next day and then making another change before allowing that to sort of coming, I think that you end up then sort of chasing your tail to try to get back in range'
>
> (Nurse Shirley, Interview 5, Lines 3816-3820)

**6.3.2.3. The dose decision**

The nurses perceived that the doctors were more cautious in deciding warfarin doses in patients with mechanical valves than those with Fontan procedure because of the risk of thrombosis. They thought that dose decisions were also dependant on the doctors' experience where some doctors' dosing was not consistent. Besides, it was thought that sometimes unnecessary dose changes made by the doctors might have resulted in fluctuations in the INR control.

> 'And sometimes there is no consistency because you know we are all individual people. Some registrars, because they are all different, they will have their own perspective and will see things you know some are much more consistent some aren't'
>
> (Nurse Madison, Interview 6, Lines 4232-4235)
>
> '… a lot of our girls will say their INR is very different when they're menstruating and actually if you just look at that pattern but you leave them on the same dose, they will return back to normal. But I think people who

> maybe aren't as familiar with them will change the dose and then you spend weeks trying to get back to where you were to get back into range'
>
> (Nurse Shirley, Interview 5, Lines 3810-3814)

Importantly, the nurses stated that there were a few families who were deciding warfarin doses themselves. They thought that these families were changing warfarin doses less frequently than the doctors. Besides, the nurses thought that the majority of these families were right in their decisions because they thought that parents know their child better than the doctor. They also stated that the doctors sometimes agreed with the dose decisions made by the parents.

> '… we've certainly got some families who are very good and will say this is what their INR is today this is what they've been having this is what I think they should have and then the doctors will say yeah that's yes I agree with that. So and [families are] usually correct'
>
> (Nurse Shirley, Interview 5, Lines 3862-3865)
>
> 'I think parents are often happier to say well actually it's dropped before, we left it at this and it just went back. Whereas I think we're probably a little bit more cautious and think OK we will change it but then often it'll be out of range though'
>
> (Nurse Shirley, Interview 5, Lines 3882-3885)
>
> 'Yes some consultants do agree the patients do their own dosing. Some say no but there are some who are quite happy because they know the parents and they think well they can do just a good job'
>
> (Nurse Madison, Interview 6, Lines 4435-4438)

#### 6.3.2.4. Adherence to the prescribed regimen

The nurses pointed out that there were a few families who were non-adherent to the prescribed warfarin dose. These families were making their own dose decisions and were altering warfarin doses less frequently than the doctors. From the nurses' perspectives, parents knew their child the best and they usually looked at the previous INR pattern of

their child when making their dose decisions and hence, they were mostly right in their decisions. The nurses also stated that sometimes the doctors agreed with the parents about their own dose decisions. In contrast, there were families who questioned the dose prescribed by the doctors. According to the nurses, these families were usually very adherent to the prescribed treatment.

> '.. parents will say well I told you that the doctor who dosed it, you know I've said to you it would go up or down, we shouldn't have done such and such, and that's where sometimes parents actually do know their child better'
>
> (Nurse Madison, Interview 6, Lines 4227-4230)
>
> 'There are a handful of families who are not compliant. And there are some families who will query what has been prescribed because they say they know their child better than the person doing the dosing… nine times out of ten the parents who do query the dose are actually the parents who are very compliant'
>
> (Nurse Madison, Interview 6, Lines 4112-4117)

Non-adherence to the prescribed regimen was thought to cause fluctuations in the INR control. This was mainly thought to be caused by missed warfarin doses, increased intake of vitamin K containing diet or excessive alcohol consumption by the adolescent patients. The nurses stated that families usually admitted missing warfarin doses, however, they did not admit taking excessive amounts of vitamin K containing diet or excessive alcohol use by the adolescent patients.

> '…parents have said have forgotten to give [the dose], they never say we've had too much of broccoli or we've had too much alcohol I mean nine times out of ten for some of my adolescent patients, I know that they've been drinking but they are not admitting to it but you just know that they are'
>
> (Nurse Madison, Interview 6, Lines 4189-4192)

### 6.3.3. Families' experience with managing warfarin therapy post cardiac surgery

Analysis of the families' interviews revealed the emergence of three main thematic areas. These included managing warfarin treatment and the coping mechanisms, warfarin dose decision and adherence to warfarin treatment.

#### 6.3.3.1. Managing warfarin treatment and the coping mechanisms

The period at the beginning of warfarin treatment was perceived to be worrying to the parents. The perceived reason behind this was the nature of the drug itself that requires close monitoring to avoid the serious adverse events. Sonya, the mother of a patient with Fontan procedure, felt anxious and uncertain about warfarin and compared it to aspirin which was previously used. Kamya, also made a comparison with aspirin regarding the dose administered where she described warfarin dose as being 'fluctuating' and 'flexible'. However, the families accepted the use of warfarin because they believed that it was very important for their children's health.

> 'I was a bit anxious because I know it takes a bit more care or attention than the aspirin that she was on. I felt a bit like I didn't really know what was to come whereas with the aspirin because she doing on it for so long we knew what to expect'
> (Mother Sonya, Interview 8, Lines 1106-1112)

> '.. it is very useful for her to take and means to thinner the bloods and for the smooth circulation of the blood so in that sense we have accepted that yeah if it is so good for [the child's] health so we'll accept it yeah'
> (Mother Kamya, Interview 11, Lines 1530-1533)

Afterwards, it was perceived that families gradually started to adapt to warfarin treatment and adjust it to the routine daily life. John, the adolescent patient, has described warfarin as part of his life when he was asked about how he felt about being involved in warfarin treatment.

> ‘I don’t mind it I suppose it’s just become part of my life really so, like I have to do it, carry on with it, so it’s like I guess eating now for me. It’s just I’m used to it so yeah that’s fine’
>
> (Patient John, Interview 2, Lines 694-653)

The day-to-day management of warfarin treatment involved many aspects. These included taking the medication, performing the INR tests and managing diet and medicines that might interact with warfarin. The information provided at the start of treatment helped the families in managing warfarin therapy. The families stated that they were provided with written information about the drug itself as well as lists of medicines and foods to avoid. According to the families, there was too much information to consider, therefore, time was required to read the information and then tailor it to the children’s daily life.

> ‘There was a long list of stuff that he [the child] could and couldn’t do… If people tell you this is what you have to do on your driving license if you look at it all and then like ooh, then actually when you get in the driver seat and you do it yourself you learn your own techniques that how to do it, don’ you? So that exactly the same as me and Evan with warfarin. We got told the list, until you take that list dissect it down take it in and then process it and do it yourself, we’ve never have a problem, have we? Since day one’ (Mother Michelle, Interview 1, Lines 225-238)

The families adopted different approaches to remember taking the medications, for example taking it with a certain meal, at a specific time of the day or using aids to remind them taking the medication. However, the families pointed out that they experienced difficulties in remembering to take the medication when it was out of the norm, for example when they had been on holidays.

> ‘…it’s easy and like we’re taking warfarin, we put that in a little pot, don’t we? for the week so it makes easy to remember taking it…. It’s when we do something that’s outside the norm you know if we go out or something rather than, because normally he [John] take it at home with his meal’
>
> (Mother Grace, Interview 2, Lines 669-692)

In addition, the dosage form of warfarin used was also very important to the families. Parents of the younger children expressed their preference of the liquid form. They believed that the liquid dosage form was more acceptable by the child, easier and more accurate to manage the prescribed dose and had better absorption and better response than the tablet form. In contrast parents of older children and the adolescent patient expressed their preference of the tablet dosage form. They expressed more convenience with taking the tablets, besides, the presence of different colours for the different tablet strengths made it easier for them to distinguish between the various strengths of warfarin tablets.

> 'She [the child] loves it which is very easy it's probably easier to adjust with liquid form than it is with a tablet I'd imagine… I don't know whether with warfarin that might be a little bit more difficult because the doses vary so much don't they?'
>
> (Mother Sonya, Interview 8, Lines 1287-1307)
>
> '… and it [INR] wasn't coming up and then Madison suggested try giving him out of the bottle, the solution, and then we went home, because I think [in] children… it seems to work better..'
>
> (Father Evan, Interview 1, Lines 356-360)
>
> 'It's just easy to get them [tablets] over and done we really just need put them in and then it's done'
>
> (Patient John, Interview 2, Lines 828-829)
>
> 'And I think with warfarin as well I mean I think the fact that there are different, the colours as well. I think that helps people with the dose as well'
>
> (Mother Grace, Interview 2, Lines 832-833)

Monitoring the INR level was a very important aspect in managing warfarin treatment. The INR test itself was described to be 'annoying' and 'bothering' to the patients at the beginning of warfarin treatment. Despite adaptation to the test afterwards, John wished to have an INR machine that does not involve finger pricking.

> '… I'm sure in about 30 years, surgery will be easier.. I guess there might be a different think of the INR machine, like easier, maybe jut you have to

> put your finger there and scan it I don't know like temperature or something'
>
> (Patient John, Interview 2, Lines 1082-1087)

The home INR monitoring was perceived to be more convenient for families, particularly for those who lived outside Leicester. The interviewed families of Group 2 patients had their own home INR monitoring machines. They felt more relieved to perform the INR tests at home because hospital INR testing would have involved travelling for long distances to perform the tests. These tests could be very frequent particularly at the beginning of warfarin treatment and also more frequent for younger children. In contrast, the interviewed families of Group 1 patients did not have home INR testing machines as they were not available to be provided at the hospital. These families lived in Leicester and they had to come to the hospital to perform the INR testing. The parents stated that they were managing to come to the hospital to perform the INR testing as it was very important to monitor warfarin treatment.

> '.. it made a lot easier have the machine at home… we were probably testing too much at the start.. could we be more nervous and anxious about is he in range, has he got having a bad day, is it because of the warfarin…'
>
> (Father Evan, Interview 1, Lines 253-260)
>
> 'It's not too bad and it doesn't bother us having to come to get it done because we know she [the child] needs it doing and I'd rather have it done than have to deal with any formal side effects with it so it's not ideal but it's not a pain'
>
> (Mother Sonya, Interview 8, Lines 1245-1253)

Managing diet and medications that might interact with warfarin action was another important aspect in managing warfarin treatment. The families emphasised the importance of having a balanced diet that would not cause significant changes in the INR values. Michelle also mentioned the importance of diet in managing the INR level particularly when it was out of the range.

> ‘At home like we’ll say if it’s [INR] really high.. I’ll go to nursery and say to them today can he have greens on his plate because then I know naturally that’s gonna help bring it down and at home we would go let’s have spaghetti bolognese and give him two pieces of garlic bread’
>
> (Mother Michelle, Interview 1, Lines 155-158)

The families were also asked about whether antibiotics’ use had caused any fluctuations in the INR control. Families of Group 2 patients stated that they had not experienced such fluctuations with the antibiotics’ use whereas families of Group 1 patients stated that their children were only newly started on warfarin treatment and they had not experienced incidents of infections that required antibiotics’ use. In contrast, Michelle believed that growth spurts had significant impact on the INR control of her child.

> ‘I think that the only time we struggle with INR dosing than anybody does.. is when he [the child] has a growth spurt because it just goes from perfect to completely out of the window.. it can go up it can go completely rock bottom..’
>
> (Mother Michelle, Interview 1, Lines 79-83)

Several concerns about warfarin treatment were raised by the families, the commonest of which was the easiness of bruising associated with warfarin treatment. This was particularly experienced by families of Group 2 patients. For John, the adolescent patient, this made him ‘more careful’ whilst performing sports. In contrast, families of Group 1 had not experienced incidents of bruising, however, they were advised to be more careful about any activities that might cause bruising.

> ‘So we’re definitely more careful we’re more aware with the warfarin than we were with the aspirin but that’s purely because we’ve been told by the professionals that the warfarin is a bit more not risky you just have to be a bit more careful’
>
> (Mother Sonya, Interview 8, Lines 1212-1216)

A different concern was raised by Kamya, the mother of an 8 year old girl from Group 1. This was her fears about the menstruation and pregnancy that her daughter would experience in the future.

> 'There was some doubts regarding this dose that when she grow young what will the problems regarding her periods regarding her pregnancy and all'
>
> (Mother Kamya, Interview 11, Lines 1864-1866)

Grace expressed several concerns about her adolescent son, John, in addition to those previously mentioned regarding bruising. She pointed out the issue of alcohol restriction that was required with warfarin treatment and hence John would have been different from his friends. In addition, she raised the issue of the cost of warfarin tablets and the strips used with the home monitoring machine that they would need to pay for after John became 18 years old. Moreover, she expressed her concerns about her son's adherence to taking his medication and performing the INR test when he was at college.

> '…and then obviously when he came to teenages and his peers are drinking and John can't drink really, so which I know it's probably minor and everything but.. that was probably the concern'
>
> (Mother Grace, Interview 2, Lines 554-561)
>
> '… I think the worst thing is if you're a bit later but he's been a teenager, you've got to go to college and you perhaps miss checking it on that day… that's the only thing that is important to do on the same day'
>
> (Mother Grace, Interview 2, Lines 656-660)

There was a perceived pivotal role of the family in managing warfarin treatment for their sons/daughters. This involved the different aspects of warfarin treatment where parents were very careful about ensuring that their sons/daughters had their warfarin doses and performed their INR tests. The parents were also careful about managing the diet and medications that may interact with warfarin and also to be careful about the activities that may put the children at risk of bruising. The family role extended to the

financial support of the adolescent to cover the cost of warfarin treatment. Besides, a very important role of the family was noticed. This was the attempts of the parent to get older children and adolescents involved and hold responsibility of managing warfarin treatment.

> '.. we can afford to pay for it, it's just a concern like you know he's lucky he's got his family that will help him find the money but [it] just concerns me that's for those people that aren't you know'
>
> (Mother Grace, Interview 2, Lines 961-963)

> 'I used to take one sentence warfarin is a tablet that thinner the bloods that circulates in the body and make your body perfect… So every day I used to explain while giving her the dose.. so in this way she has come to know everything about what is warfarin and what is going on'
>
> (Mother Kamya, Interview 11, Lines 1949-1958)

Importantly, the family role extended to the self-management of warfarin dosing and monitoring. Michelle and Evan felt very confident in their self-management of warfarin dosing and INR monitoring for their child. They also felt that they were better than the doctors because they lived with their child, knew all his habits and were aware of any change in his eating habits or health status that might influence his INR control. However, they stated that they were careful in deciding the warfarin dose and that they had discussed the suggested dose with the doctors. In addition, they stated that they were cautious in monitoring the INR where they were testing the INR sooner than was recommended when the INR was out of the range.

> 'I say we know, it's quite cheeky but I say we know how to handle [the child's] warfarin better than when we ring the consultant sometimes because we know what he is like in himself in a day, we know what he's had to eat, we know if he's not feeling particularly well, we know all of his traits. And that can sometimes trigger that his INRs fluctuates or how often we should

test. Whereas the consultants differ on that opinion, they're not with him all the time'

(Mother Michelle, Interview 1, Lines 19-26)

'Well a lot of the time we would discuss it with the consultants and Madison will sure say OK what did you give and what's his range she's actually, I'll let them know and then come back the next day and they go OK you were right then..'

(Father Evan, Interview 1, Lines 331-335)

Another important aspect of managing warfarin treatment was the communication between families and health care professionals. A good relationship was perceived to exist between the families and both the doctors and the nurses in the hospital as well as with the local general practitioner (GP) clinics and pharmacies. Kamya stated that she discussed her concerns about her daughter's future menstruation and pregnancies with the nurse Madison. Besides, both Kamya and Sonya expressed their satisfaction with the nurses being flexible about arranging the INR testing times in the hospital. In addition, the families had expressed their satisfaction with the local GP clinics and pharmacies regarding supplying them with warfarin and also regarding answering any queries about the drug.

'.. Madison has explained [to] me that when she grows, at that time may occur excess bleeding due to warfarin when she gets pregnant, then warfarin is not good for the foetus. So at that time they will suggest what treatment… or what procedure they have to follow'

(Mother Kamya, Interview 11, Lines 1867-1872)

'Well the liaison nurses have been really good about it... and they've [said] if we just come straight from school then whenever we get here we get here and that's when they do it so they've been good about it so she's not had to miss any school so far'

(Mother Sonya, Interview 8, Lines 1255-1260)

> ‘So we’ve kind of got the easier route because our GP is amazing and he said whatever [the child] needs, [the child] can have I will prescribe it, it doesn’t bother me, so he was like liquid warfarin? yeah no problem, it might cost me however many hundreds of pounds a bottle but if that’s what he needs, that’s what he’s having’
>
> (Mother Michelle, Interview 1, Lines 374-379)

#### 6.3.3.2. Warfarin dose decision

The responsibility of deciding warfarin dose was discussed with the families. Three out of the four families interviewed agreed that the best judge for deciding warfarin dosing were the doctors. These families preferred that a professional experienced with managing warfarin treatment takes the responsibility of making the dose decision. Grace further explained that managing warfarin treatment for a long time could give the families the experience in manipulating warfarin dose, however, she preferred that an expert with warfarin dosing makes the dose decision to ensure safety.

> ‘Well the doctors, I presume yeah I assume I mean they’re the ones that do it, they seem to know… because when you have the conditions I know I haven’t but John has you do get used to managing, however, from a safety point of view the doctors are always the best to dose it’
>
> (Mother Grace, Interview 2, Lines 698-707)

In contrast, Michelle and Evan thought that the parents were the best judge of deciding warfarin dose. They felt very confident in their own dose decisions and thought that they were better than the doctors in deciding warfarin dose. They explained that they knew their child better than the doctors because they were living with him and hence they knew his day-to-day eating habits, his general health status and what could cause disturbance in his INR control like the growth spurts. They further added that it was very difficult to convey all this information through a message left on an answer machine to the busy nurses that would in turn convey it to the doctors. The parents, however, added that they

would discuss the warfarin dose with the doctors and suggested that communication with the doctors be improved so that parents could convey all the information required to get the best dose decision.

> ‘It’s very rare that we are not correct, isn’t it?... because we know what he’s eaten we know how much sleep he had we know if he’s a bit under the weather that’s really hard to get across on an answer machine saying it’s 2.7, it’s really hard to understand that which is difficult’
>
> (Father Evan, Interview 1, Lines 43-48)
>
> ‘.. they have so many hundreds of, I’m sure there is so many hundreds of patients that ring up with their INRs dosages everyday so there isn’t much information you can give over the phone, whether they’ll be there all the day’ 502-506
>
> (Mother Michelle, Interview 1, Lines 503-507)
>
> ‘I think when they’re leaving an answering message, it’s kind of like there should be sort of like key factors that are ticked in the box to say he’s generally well, he’s generally not fine so we know that that dosage is gonna stay on an equal basis because then you’re adding more than one factor as a variant..’
>
> (Mother Michelle, Interview 1, Lines 509-515)

#### 6.3.3.3. Adherence to warfarin treatment

There were several factors that were perceived to influence adherence to warfarin treatment in children after congenital heart surgery. First, the importance of warfarin as an anticoagulant drug that was required to prevent clot formation was perceived to be very important. The period at the beginning of warfarin treatment was perceived to be worrying to the parents because of the nature of the new drug that was introduced to them. However, families were aware of the pivotal importance of this drug in preventing clot formation which had affected their acceptance of the drug and adherence to it (Section 6.3.3.1).

At the beginning of warfarin treatment, the families were provided with manuals and handouts that contained information about warfarin as well as the medicines and foods that had potential interactions with it. It was perceived that there was excessive information provided and that families needed time to read this information and then adjust it to the child's daily life. However, this information was described as being easy to understand and helpful to provide information about warfarin.

> 'I found it quite helpful because there was a lot of things about the warfarin that I didn't really know, and it also helped to have that information because she started school this year so it helped with having something written to pass on to school so they can see it but yeah it filled a few gaps in for us once would sat and read it…'
>
> (Mother Sonya, Interview 8, Lines 1155-1160)

The families then developed their own strategies to adjust to warfarin treatment. These ranged from strategies to remember taking the dose, manage to perform the INR tests, managing diet, restricting alcohol intake for adolescent patients and taking prophylactic measures to avoid incidents that may predispose to bruising and bleeding.

In addition, warfarin treatment regimen was also perceived to influence adherence to warfarin treatment. This included the dosage regimen and the dosage form of warfarin used as well as the INR monitoring. Besides, managing diet and restricting alcohol intake in adolescent patients was pivotal in managing warfarin treatment.

Families explained that once daily dosing was easy to manage and different families had developed different strategies as reminders. For example, taking the drug with a particular meal or at a particular time of the day or the use of aids like pots to remind them to take the drug. However, there were some concerns about missing warfarin doses when it was out of the usual daily routines, for example during holidays (Section 6.3.3.1). Regarding

the dosage form used, families of younger children expressed more convenience with the liquid dosage form of warfarin as they thought that it was more palatable, easier and more accurate when manipulating the dose and it had better absorption and better response than the tablet dosage form. Conversely, families of the older child and the adolescent patient expressed their convenience with the tablet dosage form that was easier to be taken. Additionally, they found it easier to distinguish between the different strengths of warfarin tablets because of the existence of different colour for those different strengths (Section 6.3.3.1).

Home INR monitoring was perceived to be more convenient for the families, particularly for those who lived outside Leicester. These families expressed their preference of the home monitoring as it precluded the difficulties of travelling to Leicester to perform the test. Evan further added that home INR monitoring enabled them to do more frequent testing at the beginning of warfarin treatment because they were anxious about keeping the INR within the target therapeutic range. In contrast, the two families who did not possess home INR testing machines and who were living in Leicester described hospital INR testing as being manageable. They also expressed their convenience with the flexibility of the testing times that was provided by the nurses (Section 6.3.3.1).

As described earlier, managing diet that might interact with warfarin was very important for stable anticoagulation. The majority of the families interviewed indicated the importance of having a balanced diet that contained balanced amounts of vitamin K containing foods. Michelle and Evan went even to say that they were using diet as a means to aid in controlling the INR when it was out of the target range. In contrast, Sonya indicated that diet did not represent an issue for her daughter as she was already not used to have excessive amounts of the foods listed in the list that she was provided with.

Besides, restriction of alcohol intake by adolescent patients was also very important for stable anticoagulation. Grace expressed her concerns about John's being different from his peer friends as he had to restrict his alcohol intake. John also commented on this point, however, he denied it to be annoying to him and even gave a positive perspective of the issue in that it would be saving money.

> John: so also with like drinks I'm not allowed to, I do drink a bit of alcohol but not enough to make me you know
>
> Grace: no, quite awake isn't it and it's at home
>
> John: yeah it's at home so I know they go well I'm not old enough to go out drinking yet but I'm sure I will always be the one carrying my friends home so that'll be alright
>
> Grace: also saves lots of money John
>
> Interviewer: so do you find this like annoying?
>
> John: no, to be honest, if you look at it at this perspective of money wise, I think it's no, I'll save a lot of money…
>
> (John and Grace, Interview 2, Lines 862-871)

It was also perceived that warfarin treatment had other implications on the patients' lives which were concerning to the families. The families were worried about the risk of bleeding associated with warfarin treatment and how easily their children could bleed. Therefore, the families stated that they needed to be very careful to avoid any incidents that may predispose to bleeding or bruising. For John, the adolescent patient, this required him to be 'more careful' whilst performing sports to avoid the risk of bleeding.

The other important factor that was perceived to influence adherence to warfarin treatment was the family role. The family was perceived to play a central role in warfarin treatment. This involved the role of the parents in ensuring that their children took their medication and performed the INR tests. It also involved ensuring that children had a

balanced diet that would not cause significant changes in the INR control. Moreover, it involved the financial support to cover the cost of treatment beyond the age of 18 years where patients usually had to afford for their own treatment. Furthermore, it involved the role of the family in trying to make their children involved in warfarin treatment so that they could hold the responsibility of managing the treatment in the future (Section 6.3.3.1).

In addition, the age of the child was another important factor to influence warfarin treatment. It was perceived that younger children were completely dependent on their parents in managing their warfarin treatment. Therefore adherence to warfarin treatment in children was perceived to be mostly dependent on their parents' adherence to it. For example, Michelle and Evan felt very confident in their self-management of warfarin treatment whereas Sonya preferred that her daughter's warfarin treatment be managed by the health care professional who possessed experience with managing warfarin treatment. In comparison, the responsibility of managing warfarin treatment was gradually transferred to the older children and adolescents as their parents made them more involved in this process. The issue of adolescents' adherence to warfarin treatment was perceived when Grace expressed her concerns about John's missing the warfarin dose or the INR test.

Moreover, communication with the health care professionals was another important factor affecting adherence to warfarin treatment. A good relationship was perceived to exist between the cardiac liaison nurses and the families. Concerns about warfarin treatment were discussed with the nurses who provided the relevant information and advice about them. Additionally, families who used to perform the INR tests at the hospital expressed their satisfaction with the flexibility of the nurses in managing the

testing times. Moreover, the families expressed their satisfaction with the local GP clinics and pharmacies in providing them with the medication as well as answering their queries about the drug itself (6.3.3.1).

Most of the families interviewed were perceived to be adherent to the prescribed regimen of warfarin that included the prescribed dose and the INR testing schedule. These families preferred to follow the doctors' advice as they were perceived to have the experience in managing warfarin treatment.

> 'It's all according to the advice of the hospital, the doctors, they say that this much dose has to be given and this day she has to check the INR, the reports of the INR has to be submitted on this day, so it is once they recommend that so and so dose and so and so days, she has to be checked then it is my responsibility that I have to carry out all this, yeah'
>
> (Mother Kamya, Interview 11, Lines 1705-1711)

Conversely, Michelle and Evan were perceived to be non-adherent to warfarin treatment. They thought that they were managing warfarin treatment sometimes even better than the doctors as they knew their child better. They also thought that there was too much information about the child's general condition to be transferred to the doctors to enable them to prescribe warfarin dose, the thing that a message left on the answer phone machine could not do. The parents also stated that they were changing the INR testing schedule according to the child's general condition. For example, to test earlier than was advised when the child was not in a good health condition. However, the parents indicated that they tended to be 'sensible' when managing warfarin treatment because of its serious adverse events and that they had sometimes discussed this dose with the doctors. In addition, they suggested to improve the communication between the doctors and the

families so that families can convey all the information required to make the best judgment of the dose.

> ‘I would say a lot of the time the consultants would give a dosage and we would say we are not quite sure about that we’ll give what we think and we’ll tell you what we’ve given and I would say 99% that we’re correct. It’s very rare that we are not correct, isn’t it?’
>
> (Father Evan, Interview 1, Lines 40-43)
>
> ‘.. I think… [it] would be better if parents in other way were told when you ring up we need to know how he is, is he eating well, what’s his INR, is there any signs of anything that is unwell and then make a judgment based on that because they are all facts that make massive difference to [the child]… and we then base what we think to give him on that’
>
> (Father Evan, Interview 1, Lines 475-482)

### 6.3.4. The experience of the doctors with the model-based warfarin treatment

The doctors’ views about the performance of the Hamberg model were sought. The model-based warfarin dosing was found to be reasonable and there was only occasionally disagreement with the model-predicted doses. From the doctors’ perspective, the model-based dosing was useful and acceptable in patients who had stable medical conditions with no complexities. These included children with Fontan procedure and those with AVR. Sarah also added that model-based dosing was useful in older children including those with Fontan procedure as well as those with mechanical heart valves. Besides, the doctors thought that model-based dosing was consistent and helped to decrease the inter-individual variability in doctors’ dosing. Moreover, the model-based dosing was thought to be faster to the patients than the usual daily process of prescribing. George even went to say that making the model available to the patients to adjust their own doses would be more convenient for them.

> ‘I think, I tend to find that the computer doses are sensible.. I think I’ve never seen any that have been absolutely crazy. I think I would sort of trust it to do much of the warfarin doses in patients who don’t have additional sort of complexities’
>
> (Dr. George, Interview 3, Lines 2721-2725)
>
> ‘… for Fontan and even for aortic valve normally it is consistent with whatever we have prescribing accepting some interpersonal variability as well, yeah so I think it is within acceptable range of difference in dosing’
>
> (Dr. Taj, Interview 7, Lines 3436-3438)
>
> ‘… so there is likelihood of more consistency or uniformity of the dosing pattern because among the doctors we have different persons prescribing so that sort of variability won’t be there’
>
> (Dr. Taj, Interview 7, Lines 3449-3451)
>
> ‘I think the computer dosing most advantage that it turns around probably a bit faster for the patients you know at the moment the system is that the parents call in the INR, one of the liaison nurses takes that down and they have to find a doctor to prescribe it, I think if you can cut that stage out, then that’ll be a lot faster…’
>
> (Dr. George, Interview 3, Lines 2745-2750)

However, the doctors pointed out that they occasionally disagreed with the model-based dosing in certain cases where having low INR values would be of more risk to the patients. These cases were mostly patients with MVR and those patients with fluctuating warfarin control. The doctors justified that in such circumstances, the model did not take into account the clinical condition of the patient, for example if there was impairment in the mechanical valve function that was very important in deciding warfarin dose. Therefore, George suggested a combined approach in such cases where model-based dosing to be combined with a clinical judgment to get the best dose for those patients. Taj also suggested to modify the target INR range used for the model dose prediction to be similar to that used by the doctors in clinical practice as described earlier in section 6.3.1.2.

> ‘The only thing where I’m very careful is mitral valve but again rarely I have to change.. so I feel it is.. quite matching what we are prescribing, it’s close to that’
>
> (Dr. Taj, Interview 7, Lines 3439-3441)
>
> **‘**I think sometimes you get a patient who got very labile doses, as long as you have an experience in prescribing it, I think probably that might be slightly more reliable because we’ve got to take a lot of additional factors into account that I think probably the warfarin dosing model doesn’t’
>
> (Dr. George, Interview 3, Lines 2725-2730)

In addition, the doctors were cautious about recommending the model to be used in clinical practice. The doctors preferred to have more experience with the new dosing approach and to wait for the study results before giving their recommendations.

> ‘I think it probably needs more time to establish… but it is difficult to say whether to be applied completely in practice.. I think it is very forward it can be a replacement…’
>
> (Dr. Taj, Interview 7, Lines 3526-3537)
>
> ‘So we have to look into the over result and the success rate and the failure rate and the maybe the rate where it had to be individually re-adjusted or didn’t agree and then we will know how much this model fit, in a scientific numbers’
>
> (Dr. Sarah, Interview 4, Lines 3039-3042)

### 6.3.5. The experience of the cardiac liaison nurses with the model-based warfarin treatment

The cardiac liaison nurses also thought that the model-based warfarin dosing performed very well for patients with Fontan procedure. Shirley thought that the model-based dosing also worked very well for some patients with mechanical heart valves whereas Madison did not like its performance in these patients. However, the nurses thought that the model-based dosing did not change the warfarin dose when the INR value

was very low. They had also added that the model-based dosing was associated with frequent INR testing, particularly in patients with mechanical heart valves.

> 'I think from what I can see is the computer dosing for patients who are on warfarin, I think they are nice and stable I think it's working really well I think for the valve patients, for some patients again it's working really well, for others, I don't think it is..'
>
> (Nurse Shirley, Interview 5, Lines 3955-3958)
>
> 'Fontan patients fantastic. It's really good. Mechanical valve patients, I don' like it… because they have to be tested much more often'
>
> (Nurse Madison, Interview 6, Lines 4287-4290)

The nurses also talked about the families' acceptance of the model-based doses. They pointed out that there were few families who had not accepted the model-based doses and preferred to give their own doses, whereas some other families had questioned the model-based doses.

> '… I think for most families they've been fine it's been fairly stable I think there are a couple who've done their own thing which obviously doesn't help the study. There are a few families who've questioned when we've said the computer doses… but when we've explained to them well it's part of the study… families have been fine with that'
>
> (Nurse Shirley, Interview 5, Lines 3962-3972)

Regarding their experience with the study, the nurses stated that the model-based dosing had not put any patient at risk and that the dosing process was done in a timely manner. However, there was the issue of missed dosing when the families were ringing during the weekends. The nurses were also cautious about recommending the model-based dosing for use in clinical practice and preferred to wait for the study results before making their recommendations.

> ‘I think for some patients it has worked. I think for others I don’t know the research may show differently maybe just be my experience from looking at the charts. I guess we have to look at the valve patients to see whether to do that proper comparison and then to see who’s more, I don’t think the computer system put anybody in danger’
>
> (Nurse Shirley, Interview 5, Lines 4013-4018)
>
> ‘I want to see the results before I say anything. I want to see the results. For Fontan patients I think it’s fine, but I want to see a hard evidence in front of me before I answer that question’
>
> (Nurse Madison, Interview 6, Lines 4454-4459)

### 6.3.6. The experience of the families with the model-based warfarin treatment

Families of Group 1 patients were generally asked about warfarin dose changes and the frequency of INR testing without mentioning the model-based approach. Sonya pointed out that her daughter’s warfarin doses were consistent and did not have any extreme changes. In contrast, she stated that the frequency of the INR testing was irregular which might be due to the fact that she was recently started on warfarin treatment, therefore, she was not stable enough to have longer periods of testing. Besides, Kamya preferred to strictly adhere to what she had been advised about warfarin doses and the INR testing schedule as she thought that this was the best for her daughter. However, it is important to note that she mentioned that she adhered to the doctors’ and hospital’s advice in this regard.

> ‘It’s fine. We’ve not had anything, her doses tend to be over a similar pattern so it’s not, we’ve not had anything drastic’
>
> (Mother Sonya, Interview 8, Lines 1278-1279)

> ‘It’s just random… I don’t know anyway because you tell us when to come back don’t you? We haven’t managed to stabilise, say like I know some

> people who come every three weeks… but they've been on warfarin quite a while whereas with [the child] she's just all over the place'
>
> (Mother Sonya, Interview 8, Lines 1237-1243)

In contrast, a second interview was conducted with families of Group 2 patients to ask them about their experience with the model-based dosing approach. John and Grace stated that John's INR control was balanced and stable within the target therapeutic range. They also added that there was not very frequent changes in warfarin doses and the INR testing schedule. Conversely, Michelle and Evan were not satisfied with the model-based warfarin dosing. They thought that the new dosing approach was associated with very long INR testing intervals and were adamant that a three-weeks testing interval was recommended to them despite that the child's INR chart did not contain such an interval. The parents also stated that the frequency of INR measurements was not consistent whereas that of the doctors' was of more consistency. Besides, they thought that the model-derived warfarin doses were very high that had led to increase the INR level above the target therapeutic range. They also felt that the INR values were more out-of-range during the Model phase than they were during the Doctor phase. The parents hence felt more comfortable with the doctors' management of warfarin dosing. They explained that parents had equal responsibility with the doctors and nurses in managing warfarin treatment for their child because they know all his day-to-day habits. They also added that the doctors and nurses used to take that into consideration, therefore, they preferred the doctors' approach for a better management of warfarin treatment for their child.

> 'and I think as well that the nurses understand that parents are just as responsible for the dosage as the clinical liaison nurse and the consultants because we're the ones who see what they clinically look like because we're at home with them and you understand your child's condition when you are a parent… and I think the nurses take that into consideration and the

consultants so if you all work on a big team we get it spot on every time with him normally and we can stay in range for months can't we?'

(Mother Michelle, Interview 9, Lines 2157-2170)

### 6.4. Discussion

This study explored for the first time the lived-experience of the doctors, nurses and patients/parents with managing warfarin treatment after congenital heart surgery. Exploration of the doctors' lived-experience with warfarin treatment provided a detailed insight into the process of warfarin dosing and INR monitoring performed in daily clinical practice. It was revealed that the indication for warfarin anticoagulation and the patient's clinical condition were the key determinants of all aspects of warfarin dosing and monitoring. Patients with MVR were of particular concern to the doctors and infants with small mechanical mitral valves were even more concerning to the doctors. Therefore, they tended to be very cautious about warfarin dosing and monitoring in patients with MVR.

During the process of INR monitoring and warfarin dose adjustments, the doctors were not worried about strictly keeping the INR values within the target therapeutic range. Instead, they accepted a wider range depending on the indication for warfarin use for more consistency in dosing. It's also important to note that the doctors were not worried about the bleeding complications associated with very high INR levels but expressed their fears of having thrombotic events with low INR levels, particularly in patients with MVR. Therefore, they were very cautious about withholding warfarin treatment when the INR levels were very high. This approach to dosing is in discrepancy with the local guidelines (Appendix 1) which recommend to adjust warfarin doses to keep the INR within the target therapeutic range and to stop warfarin treatment when the INR value is above 4.5. The doctors agreed the existence of guidelines for warfarin dosing and monitoring, however,

they pointed out that they were individualised according to the patient's clinical condition.

In addition, it was revealed that maintaining the INR within the target therapeutic range was most difficult in two groups of patients, those below 5 years of age and adolescent patients. The results of Group 2 patients demonstrated in Chapter 5 Section 5.3.2.8 also showed that patients aged 1 to 5 years had the lowest time in therapeutic range among all age groups, though this was not statistically significant. However, patients aged 11 to 18 years were shown to have the highest time in therapeutic range but it was also not statistically significant.

Moreover, the doctors described the INR control in patients with Fontan procedure as being stable compared to patients with mechanical heart valves, particularly those with MVR. The fluctuating INR control in patients with mechanical valves was attributed to the more frequent INR monitoring in this group. The results of Group 2 patients (Chapter 5 Section 5.3.2.8) also demonstrated that patients with Fontan procedure had statistically significantly higher time in therapeutic range as compared to those with mechanical heart valves.

To our knowledge, there is no study to date that has explored the lived-experience of doctors with managing warfarin treatment in congenital heart surgery. The doctors' experience of managing warfarin treatment in elderly patients with atrial fibrillation has been investigated (Bajorek et al., 2007; Borg Xuereb, Shaw and Lane, 2016). However, the main focus was on the need for customised information to aid in decision-making about initiating warfarin treatment in these patients as well as to enhance the day-to-day management of warfarin (Bajorek et al., 2007; Borg Xuereb, Shaw and Lane, 2016).

Another study explored the physicians' experience with communicating the diagnosis of atrial fibrillation and the need for warfarin use, decision-making of warfarin use and the systemic barriers for communicating information (Borg Xuereb, Shaw and Lane, 2016).

Exploration of the experience of the cardiac liaison nurses provided another insight into the process of warfarin dosing and monitoring. The nurses described their role in the process and complained of the time consumed during it. Taking into account their other work responsibilities, the nurses lacked the time required to have proper communication with families during the daily monitoring process. Therefore, the nurses expressed their need for a dedicated anticoagulation service for better communication with families which in turn can enhance warfarin treatment. Implementation of anticoagulation clinics for children has been shown to improve management of warfarin treatment in this population (Murray et al., 2015; Newall et al., 2004). A patient-centred service that was dedicated for paediatric cardiology patients was not only shown to improve the time in therapeutic range but also to be associated with high satisfaction of the patients and providers (Murray et al., 2015).

The major forms of non-adherence to warfarin treatment, as described by the nurses, were non-adherence to the prescribed dose, missing the dose, excessive intake of vitamin K containing diet and increased alcohol consumption by the adolescent patients.

No study, to date, has explored nurses' experience with managing warfarin treatment in children after congenital heart surgery. However, the nurses' perspectives about warfarin use in elderly patients were explored (Bajorek et al., 2006). In this study, the nurses talked about the patients' attitudes towards warfarin treatment, the barriers to using warfarin in elderly patients, the process involved during initiation of warfarin treatment, their limited

role in managing warfarin treatment and how to improve the use of warfarin in this population.

Exploring the perspectives of patients/parents also provided a very important insight into the long-term management of warfarin treatment after congenital heart surgery. The period at the beginning of warfarin treatment was felt to be more worrying to the parents because of the nature of the new drug being introduced to the treatment. Despite being excessive and requiring time to be considered, the information provided at the beginning of the treatment was perceived to be helpful to the families for the day-to-day management of warfarin treatment. In a study in elderly patients with atrial fibrillation, both patients and physicians perceived the lack of information required for managing warfarin treatment, particularly that concerning the drug interactions and vitamin K containing diet (Bajorek et al., 2007).

There were several factors that were perceived to influence the families' adherence to warfarin treatment. First, because of the vital importance of the drug for the patients' medical condition, the families accepted warfarin and developed their own strategies to adjust it to their daily life. Adjustment to disease and treatment regimen was shown to affect adherence. In children and adolescents with end-stage renal disease, poor adjustment to disease and dialysis was one of the factors that correlated with low levels of adherence to treatment (Brownbridge and Fielding, 1994).

Second, age was also viewed as another important factor affecting adherence to warfarin treatment. Young children were felt to be completely dependent on their parents to manage their warfarin treatment. This ranged from a family that was strictly adhering to the prescribed regimen to a family that claimed more parental responsibility in deciding

warfarin doses. In contrast, in older children and adolescents, attempts were made to make them more involved and responsible about managing their own treatment. The non-adherence issues encountered in this age group were mostly regarding missing the dosing/monitoring of the drug and restriction of alcohol intake as described by the doctors, nurses and the parent of the teenager patient. In a study of warfarin therapy in children, the more likely cause of having non-therapeutic INR levels in patients older than 15 years was shown to be the omitted doses of warfarin (Newall et al., 2004).

Third, family factors were another important influence on adherence to warfarin treatment. The parents were perceived to be supportive to their children and engaged in managing their warfarin treatment. Besides, it was felt that there was a team-based family management to adapt warfarin into the routine daily life of the child. Such cohesive family environments has been shown to enhance adherence in children and adolescents (Pereira et al., 2008).

Fourth, the treatment regimen was another essential factor affecting adherence to warfarin therapy. The once daily dosage was perceived to be convenient for the families. However, there were different preferences of the dosage form used according to the patients' ages. In addition, home INR monitoring was felt to be more convenient for the families, however, hospital INR monitoring was also manageable by the families. In a previous study on children with congenital heart disease, families expressed their dissatisfaction with hospital INR monitoring because it involved time off school/work, cost of travelling and inconvenience of venepuncture (Duggan, Pearce and Guilbert, 2001). In contrast, home INR monitoring of children on long-term oral anticoagulation was felt to be easily managed by the families. Additionally, it provided a feeling of empowerment as families had more control and involvement in the drug monitoring process. Moreover, it saved the

time and reduced stress and anxiety encountered in hospital monitoring (Jones et al., 2013). Furthermore, it is highly accurate and reproducible (Jackson et al., 2004).

Fifth, the relationship with the health care provider was also essential in enhancing adherence. Good communication was felt to exist between the families and the doctors and nurses in the hospital as well as the local GP clinics and pharmacists. Effective communication between the families and the health care providers can significantly improve adherence to the prescribed regimen which is especially important in patients with chronic diseases (Brand, Klok and Kaptein, 2013).

An important aspect in the process of warfarin dosing and monitoring was making dose decisions subsequent to changes in the INR values. Three of the families interviewed felt safer when people experienced with managing warfarin treatment took the responsibility of making dose decisions. This may be attributable to the high level of families' trust in the doctors' medical experience, hence they were relying on the doctors in warfarin dose decision-making. In contrast, a different attitude was expressed by one family where the parents thought that it's the parents' responsibility to take this decision as they know their child sometimes better than the doctors. This attitude reflects the parents' claims to be involved in decision-making based on their experience in managing warfarin treatment for their child. Interestingly, the nurses agreed that families who used to make dose decisions were usually right and they also used the term 'they know the child the best'. These two different attitudes towards warfarin dose decision demonstrate the difference between adherence; where there is minimal input in treatment decision making (Bosworth, Weinberger and Oddone, 2006) and concordance which involves the patients' participation in treatment decision-making (Britten N and Weiss M, 2004). It is therefore

important to understand the different attitudes and perspectives of the families to enhance warfarin treatment.

The experience of older patients with warfarin treatment has been explored (Dantas et al., 2004; Wild, Murray and Donatti, 2009). In a study to explore the perspectives of elderly patients about warfarin treatment, the participants tended to have a minimal role in decision-making regarding initiating warfarin treatment. Instead, they were more dependent on the physicians' experience to make this decision. Besides, there was a perceived low level of knowledge about the drug by the authors. Moreover, the participants reported a low impact of warfarin on their daily lives and expressed satisfaction with the care provided (Dantas et al., 2004). In contrast, in another study of old patients on oral anticoagulation, the participants found that the treatment was troublesome, particularly that regarding the INR monitoring and the restriction of diet and alcohol. However, the participants accepted the restrictions of the oral anticoagulant treatment and the adjustments that it required in their daily life (Wild, Murray and Donatti, 2009).

Regarding their experience with the model-based warfarin dosing approach, the doctors found the new approach useful and acceptable in patients with stable medical conditions. These were generally older children and patients with Fontan procedure and AVR. They also thought the new dosing approach was more consistent and time saving. Additionally, there was only occasional disagreement with the model-derived doses where the doctors preferred to have more clinical input which was mostly in patients with MVR. Results of Group 1 patients demonstrated in Chapter 4 Section 4.3.2.8 have shown that doses were overridden in only 1.9% of the dose recommendations made by the model. In addition, results of Group 2 patients demonstrated in Chapter 5 Section 5.3.2.9 have

shown that doses were overridden in only 3.9% of the dose recommendations made by the model. The nurses also favoured the model-based dosing for use in patients with Fontan procedure. However, both doctors and nurses were cautious about recommending the new dosing approach for use in clinical practice. They preferred to have more experience with the new approach and to wait for the study results before making their recommendations.

From the families' perspective, there was only one family where the parents expressed their dissatisfaction with the model-predicted doses as well as the inconsistency of the INR testing schedule. They have further added that their child's warfarin treatment was better controlled by the doctors and hence they preferred the doctors' approach. However, these parents' accounts were contrasting to their perspectives that were initially disclosed during the first interview where they stated that it's the parents' responsibility to manage the warfarin treatment for their child. Additionally, their accounts about the model-based doses and INR testing schedules and the comparisons that they made with the doctors' approach were incorrect. Moreover, in terms of warfarin control for this child, he had better control during the Model phase than the Doctor phase of treatment as indicated by both the percentage of INR values within the target range (%ITR) and the percentage of time within the target range (%TTR). The %ITR for this child was 51.6% and 39.1% in the Model phase and the Doctor phase, respectively, and the %TTR was 69.2% and 53.8% in the Model phase and the Doctor phase, respectively. The perspective obtained from this family may be due to their inability to discuss the model-based doses whereas they were able to discuss and change the doses recommended by the doctors.

A limitation to this study was the small sample size and hence, the selected sample may not have been representative of the population. Other potential participants that could

have been included are more families whose children requiring very frequent INR testing, more teenager patients and junior medical staff. However, interpretative phenomenological analysis (IPA) is usually based on small samples as the issue is the quality of data, not quantity (Smith, Flowers and Larkin, 2009). In addition, this qualitative study was designed to be complimentary to the quantitative study to explore the views of families and health care providres about warfarin treatment and the new dosing approach and the limited time and resources available for the study precluded a larger sample size.

This study provided a very important insight into the experience of doctors, nurses and patients/parents with the day-to-day management of warfarin treatment. Their perspectives about the model-based warfarin dosing approach provided a very important idea about the acceptability of the new dosing approach and strategies to improve its clinical applicability. Additionally, it also highlighted a very important barrier to its clinical use which is the families' adherence to the model-derived doses.

# *Chapter Seven*

# *General Discussion*

# Chapter 7: General Discussion

This research project has for the very first time prospectively evaluated in routine clinical practice, personalised warfarin dosing using a PK/PD model. The study timeline is demonstrated in Appendix 8.

The first step in this project, and prior to the prospective clinical study was to assess the predictive performance of the Hamberg model in a cohort of 60 post-operative cardiac children on long-term warfarin treatment at the EMCHC. Seventy percent of the predicted doses were ideal (within 20% of the observed doses) with a bias of -0.10 and precision of 0.19. The predictive performance of the Hamberg model was previously evaluated in a cohort of 49 children on warfarin treatment (Hamberg et al., 2013). The ideal dose prediction was also 70%, but the bias was -0.04 and the precision was 0.57. The results of clinical accuracy (ideal dose prediction) obtained from the present study was therefore similar to that obtained by Hamberg *et al* (2013) but the bias was higher (-0.10 in the present study compared to -0.04 in the Hamberg *et al* (2013)). This implies a dose underprediction of 0.1 mg compared to 0.04 mg, respectively. Conversely, the dose predictions were more precise (0.19 vs. 0.57) in the present study compared to the Hamberg *et al* (2013) evaluation. Therefore, the results obtained from the present study provided adequate validation of the model for use in children in the EMCHC and gave reassurance for the prospective evaluation of the model in routine clinical practice to be started.

The next step in this research project was the prospective clinical evaluation of the PK/PD model in routine clinical practice in two groups of patients. Group 1 included five patients starting warfarin treatment for the first time after congenital heart surgery. The results of

this study showed that model-based warfarin dosing resulted in 22.6% greater percentage of INR measurements within the target therapeutic range (%ITR) and also about 21% greater percentage of time within this range (%TTR). In addition, model-based warfarin dosing resulted in a longer time before over-anticoagulation occurred, fewer over-anticoagulated patients and shorter time to reach stable anticoagulation when compared with the traditional dosing approach. However, the time to reach a therapeutic INR was 3 days longer using the model-based dosing approach when compared to the traditional dosing approach.

Group 2 included 26 patients who were maintained on long-term warfarin treatment. The overall analysis of the %ITR and the %TTR between the model-based approach and the traditional dosing approach showed small improvements in both %ITR (mean difference 0.92%, $p = 0.84$) and %TTR (mean difference 5.27%, $p = 0.09$), though these were not statistically significant. However, the %TTR of the model-based approach was statistically significantly higher than that of the traditional approach ($p = 0.03$) after excluding 5 patients who experienced medical issues during either phase of treatment. Interestingly, the sub-group analysis showed that the %TTR was statistically significantly higher in patients with Fontan procedure using the model-based approach than by using the traditional approach after excluding the 5 cases with medical issues. In addition, the %TTR in patients with mechanical heart valves was also improved by using the model-based dosing approach, though this was not statistically significant (mean difference 4.1%, $p = 0.51$). In addition, the frequency of INR measurements per month was comparable between the two treatment approaches. Moreover, the model-based approach was associated with lower levels of over-anticoagulation when compared to the traditional approach, although this was not statistically significant. However, the number

of dose changes was statistically significantly higher in the model-based approach when compared to the traditional dosing approach. This was because of the method of dose estimation by the model where it adjusts the dose to the mid-value of the target INR range. Thus, the model may recommend unnecessary dose changes for only slight changes in the INR observations which may not be clinically significant.

The PK/PD model-based warfarin dosing that takes into account the effect of genetic and non-genetic factors on warfarin PK and PD was never tested clinically, on a prospective basis in children. However, genotype-guided warfarin dosing was previously investigated in children starting warfarin treatment (Tabib et al., 2015). The study revealed that genotype-guided dosing of warfarin significantly decreased the time to stable dose and hospital stay days but found no difference in time to first therapeutic INR, time before over-anticoagulation occurred and bleeding events when compared with the standard dosing approach (Tabib et al., 2015). In addition, genotype-guided warfarin dosing was also investigated in adults starting warfarin treatment (Pirmohamed et al., 2013). The study revealed that genotype-based dosing of warfarin has resulted in significantly higher proportion of time in therapeutic INR range, fewer incidents of over-anticoagulation and shorter time to therapeutic INR than the standard dosing approach. Moreover, the PK/PD model-based warfarin dosing was investigated in adults and was shown to result in significantly higher proportion of time in target therapeutic range, lower proportion of out-of-range INR values and shorter time to first therapeutic INR and stable anticoagulation when compared to the genotype-guided dosing (Perlstein et al., 2012). Furthermore, the PK/PD model-based personalised dosing has previously been shown to improve the clinical outcome and reduce adverse events of other narrow therapeutic range drugs used in children. One such example is busulfan, an alkylating agent that is used

prior to haematopoietic stem cell transplantation (Copelan et al., 1991). Busulfan is a narrow therapeutic range drug that has wide PK inter-individual variability which was attributed to multiple demographic, genetic and clinical factors (Bertholle-Bonnet et al., 2007; Beumer et al., 2014; Choi et al., 2015; Hassan et al., 1994). Therefore, it is pivotal to individualise busulfan treatment to avoid both serious liver toxicity (veno-occlusive disease; VOD), and graft rejection (Slattery et al., 1995). A model-based approach was implemented to individualise oral busulfan treatment in bone marrow transplantation children (Bleyzac et al., 2001). The study showed that decreased busulfan doses were required in 69% of patients compared to the conventional doses. The researchers also reported that the incidence of VOD was significantly lower than the control group and the VOD-free survival was significantly higher than the control group. Moreover, the engraftment was successful in all patients who received the adjusted dosage regimen whereas graft failure occurred in 12% of the control subjects (Bleyzac et al., 2001). Hence, it can be concluded that the model-based dose adjustment of drugs with narrow therapeutic range can result in more accurate dosing, decreased incidence of serious adverse events and improvement of treatment outcome.

The qualitative part of this research project involved exploring the experience of doctors, nurses and families with managing warfarin treatment as well as their views about the new dosing approach of warfarin. The doctors provided a detailed insight into the process of warfarin dosing and monitoring performed in usual clinical practice. They revealed that the indication for warfarin use and the patient's clinical condition were the key determinants of all aspects of this process where patients with mechanical mitral valves were of particular concern to them. During the dosing/monitoring process, the doctors were not worried about strictly keeping the INR values within the target

therapeutic range and adopted a wider range depending on the indication for warfarin use for more consistency in dosing. In addition, there were less concerns about the bleeding complications associated with very high INR levels than about the thrombotic events associated with low INR levels, particularly in patients with mechanical mitral valves. Moreover, the doctors revealed that INR control was most difficult in of patients below 5 years of age and adolescents.

The cardiac liaison nurses provided another insight into the process of warfarin dosing and monitoring. They described their role in the process and felt that it was time-consuming. Therefore, they expressed the need for a dedicated anticoagulation service for better communication with families, which in turn can enhance warfarin treatment. The nurses also thought that home INR monitoring was more convenient than the hospital monitoring for most of the families. In addition, the major forms of non-adherence to warfarin treatment, as described by the nurses, were non-adherence to the prescribed dose, missing the dose, excessive intake of vitamin K containing diet and increased alcohol consumption by the adolescent patients.

The experience of the doctors and nurses with the model-based warfarin treatment was also investigated. There was an overall acceptance of the new dosing approach particularly in stable patients who were mostly those with Fontan procedure. However, the doctors recommended that model-based dosing is accompanied by clinicians' judgment in patients who have medical complexities. In addition, they suggested the use of target INR ranges similar to those used in clinical practice to enhance the clinical utility of the model. Moreover, both doctors and nurses preferred to have more experience with the model-based warfarin treatment and to wait for the study results before recommending it for use in the usual clinical practice. This may be because in order to apply a new

intervention in clinical practice, evidence-based information about its safety and efficacy is required to support its clinical use.

To our knowledge, this is the first study exploring the experience of the doctors and nurses with managing warfarin treatment in children after congenital heart surgery. Doctors' and nurses' experience of managing warfarin treatment in elderly patients with atrial fibrillation has been previously investigated (Borg Xuereb, Shaw and Lane, 2016; Bajorek et al., 2006). However, the focus was on the physicians' experience with communication with elderly patients (Borg Xuereb, Shaw and Lane, 2016), whereas the nurses provided their perspectives about these patients and the use of warfarin in this population (Bajorek et al., 2006). Obtaining a detailed insight into the process of warfarin dosing/monitoring performed in usul clinical practice and the views about the new dosing approach is very important to enhance the clinical utility of the model-based warfarin dosing in children in the future.

The families' experience with managing warfarin treatment was also explored. The period at the beginning of warfarin treatment was felt to be more worrying to the parents. However, with the aid of the provided information, the families then started to adopt different strategies to enhance the daily management of warfarin treatment. Several factors were perceived to influence the families' adherence to warfarin treatment. These included the importance of the drug for the patients' medical condition, patient's age, treatment regimen, family role and relationship with the healthcare providers. The families also provided their views of warfarin dose decision. Three of the families interviewed felt safer when an expert with warfarin dosing/monitoring took the responsibility of making dose decisions. In contrast, one family expressed a different attitude where the parents thought that it is the parents' responsibility to take this decision,

and consequently they were opposed to the model-based warfarin dosing approach. These two different attitudes towards warfarin dose decision demonstrate the difference between adherence; where patients are usually required to follow the advice of the healthcare provider with minimal input in treatment decision making (Bosworth, Weinberger and Oddone, 2006) and concordance which involves the patients' participation in treatment decision-making (Britten N and Weiss M, 2004).

One study has investigated the impact of warfarin treatment on children with congenital heart disease and their parents focusing mainly on INR monitoring in the hospital (Duggan, Pearce and Guilbert, 2001). Patients/parents expressed their dissatisfaction with hospital monitoring as it involved time off school/work, travelling cost and inconvenience of venepuncture. In addition, both children and parents expressed their concerns about the risk of bleeding and the responsibility of ensuring regular intake of the medication and keeping the INR within the target therapeutic range (Duggan, Pearce and Guilbert, 2001). Obtaining the families' perspectives is very important to enhance warfarin treatment in children. In addition, understanding their attitudes about dose decision-making and the new dosing approach is pivotal for the future implementation of the model-based warfarin dosing in clinical practice.

The results obtained from the present study have shown that the PK/PD model performed very well in the clinical setting. This was reflected not only by demonstrating an improvement in the time within therapeutic range but also by virtue of overall acceptance of health care prpfessionals to the principles and clinical practice of allowing a model-based dosing approach as a basis for predicting the most optimum doses of warfarin. This was demonstrated quantitatively by showing that only about 6% of the model-predicted doses were overridden by the doctors. In addition, the qualitative

research indicated the acceptance of both doctors and nurses to the use of the model-based dosing approach in patients with stable medical conditions. This acceptance was also reflected through the doctors' suggestions to enhane the clinical utility of the new dosing approach.

Clinically, these findings demonstrate that the new model can improve the anticoagulation control of warfarin and hence can result in minimising potentially serious adverse events such as bleeding or, conversely, thrombosis. The model, therefore, can potentially reduce the number of hospital admissions that occur due to the need to administer intravenous heparin to patients who are under-coagulated or conversely, for those with elevated INR levels, admission to administer vitamin K. The results obtained from the largest cohort of children on warfarin treatment has shown that the incidence of serious bleeding events was 0.5% per patient year whereas that of recurrent thrombosis was 1.3% per patient year (Streif et al., 1999).

The study findings also suggest that the model-based warfarin dosing is more likely to be beneficial in patients starting warfarin for the first time after congenital heart surgery. In addition, for patients who are on maintenance warfarin treatment, those with Fontan circulation who represent the majority of the population at the EMCHC, are more likely to benefit from the new dosing approach. Moreover, these findings are likely to replicated at other centres, however, further work is required to demonstrate that. Furthermore, if this study was repeated at the EMCHC, the findings could have been further improved if the target INR range used for dose estimation was interpreted using the same approach as doctors, i.e. that it is not rigid and fixed, but rather flexible and dependent on the clinical condition of the patient at the time. The current research findings are supportive of the pivotal importance of the model-based personalised dosing in improving the clinical

outcomes and reducing the adverse events of drugs with a narrow therapeutic range. It extends the current knowledge on the importance of adopting the model-based dosing approach of warfarin in children after congenital heart surgery in clinical practice to enhance the drug's anticoagulation control and reduce its adverse events. Therefore, it is important to demonstrate the advantages and drawbacks of the application of the PK/PD warfarin dosing model in clinical practice. Next, the necessary steps before the application of the model-based warfarin dosing can be introduced in clinical practice will also be considered.

### 7.1. Advantages and drawbacks of the application of the PK/PD model in clinical practice

The clinical application of the PK/PD model had its advantages and drawbacks. The dose prediction by the model was easily performed by the researcher for both *a priori* and *a posteriori* dose estimation. Additionally, there was more accuracy and consistency in warfarin dosing which may help in reducing the inter-individual variability in doctors' dosing. Moreover, as indicated in the nurses' accounts, the process was relatively rapid, hence this can reduce the time required for warfarin prescribing in routine clinical practice. Furthermore, the use of point of care genotyping of CYP2C9 and VKORC1 provided rapid turnaround of the genotype results (Howard et al., 2011) which was particularly important for Group 1 patients. However, *a posteriori* dose prediction requires the patient's INR history to be imported from Excel files that have specific requirements of file naming and data format. These files are time-consuming when initiated particularly for patients with very frequent INR testing. In addition, the plot of the predicted and observed INR values needs to be assessed to obtain the best individual fit of the curve for the best dose prediction which needs some understanding of the

underlying model and the prediction process. Moreover, the model uses the mean of the target INR range for dose adjustment which has led to more frequent dose changes which potentially may not be convenient for the families. Indeed, the use of the mean of the target range sometimes led to dose predictions that were overridden by the doctors, particularly in patients with MVR where the doctors favoured to keep slightly high INR values. Furthermore, the dose estimation was mostly performed by the researcher and occasionally by the clinical supervisor who had dedicated time for this research. This process was very challenging for one person to be responsible for it because patients could ring the INR test results or come to the hospital for INR testing at any time in or outside the working hours/days.

Therefore, to implement a PK/PD model-based personalised dosing approach in clinical practice requires several additional steps, which will be discussed in the next section.

### 7.2. Necessary steps to enhance the implementation of the PK/PD model in clinical practice

In order to enhance the clinical implementation of the PK/PD model, several steps are required. First, the predictive performance of the model needs to be enhanced where dose estimations should be adjusted to the entire target INR range and not to the mid-value as is currently the case. In addition, the use of a wider target INR range similar to that used by the doctors in routine clinical practice is important for more consistent dosing and to avoid the risk of under-dosing.

Second, the entire process would benefit from being performed electronically for more convenient use. This involves using electronic medical records and electronic INR charts into which the model can be integrated. An electronic system could generate reminders

and prompts of when dose adjustments are required as well as prompts for clinicians to approve the dose recommended by the model.

Third, pharmacists and doctors are required to be trained to use the model as the process of warfarin dosing and monitoring can take place at any time within or outside the working hours/days.

Fourth, point of care genetic testing of CYP2C9 and VKORC1 is recommended for rapid achievement of genotype results. However, this process will involve technical challenges in establishing such electronic systems in addition to the administrative challenges encountered in approving the new dosing approach for use in clinical practice as well as obtaining the acceptance of the medical personnel to be involved in this process.

### 7.3. Recommendations for future research

This research project has shown that the model-based warfarin dosing can improve the anticoagulation control in children with congenital heart disease. The study was limited by its small sample size, which meant that statistically significant improvements could not be demonstrated for most of the measured outcomes. However, given the results of the sub-group analyses and the totality of the data, there is sufficient evidence to suggest a positive benefit and hence a multi-centre randomised controlled clinical trial to evaluate the clinical effectiveness of the model-based warfarin dosing in children after congenital heart surgery should be conducted.

A larger sample size that includes a greater number of children with mechanical heart valves and more children with variant alleles of CYP2C9 and VKORC1 would provide a more conclusive evaluation of the model-based warfarin dosing. This would also provide a better understanding of the effects of genetic and non-genetic factors on warfarin dose

requirement and time in therapeutic range in children on long-term warfarin treatment. In addition to the evaluation of the clinical utility of the model-based warfarin dosing, an economic evaluation of the new dosing approach is also required. Therefore, a pharmacoeconomic study which evaluates the cost of the model-based, genotype-guided dosing of warfarin and outcomes such as the incidence of major bleeding and thrombotic events and hospital admissions for intravenous heparin or vitamin K use is essential to inform decision about the wide use of the new dosing approach in clinical practice.

### 7.4. Conclusions

This research project has extended the current knowledge on the clinical application of the model-based, genotype-guided warfarin dosing in children after congenital heart surgery. The new dosing approach can improve the anticoagulation control which is more likely to be beneficial in children starting warfarin for the first time after congenital heart surgery as well as children with Fontan circulation who are maintained on long-term warfarin treatment. Besides, it has demonstrated the overall acceptance of the healthcare professionals of the new dosing approach. Moreover, it has provided an in-depth understanding of how warfarin treatment is managed in routine clinical practice and the challenges encountered in this process. Furthermore, an understanding of how families handle long-term warfarin treatment was obtained. However, further work is required to establish the clinical effectiveness and cost-effectiveness of the new dosing approach in this group of children.

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# Appendices

## Appendix 1: East Midlands Congenital Heart Centre guidelines for paediatric warfarin dosing

### DOSING

| | | |
|---|---|---|
| Initial dosing (day 1) | | |
| If INR baseline is 1.0 – 1.3, start with 0.2 mg/kg orally (maximum of 10mg)<br>If INR baseline is more than 1.3 reduce loading dose to 0.1 mg/kg | | |
| Measure INR Day 2 – 6 | | |
| If your response is an INR of | | |
| INR | 1.1-1.4 | Repeat loading dose |
| INR | 1.4-1.9 | 50% of loading dose |
| INR | 2.0-3.0 | 50% of loading dose |
| INR | 3.0-4.0 | 25% of loading dose |
| INR | >4.5 | Omit dose until INR less than 4.5 then restart at 50% less than previous dose |
| If INR not greater than 1.5 on day 4 contact consultant haematologist for help | | |
| Long term control – day 6 onward | | |
| INR | 1.1-1.4 | Increase by 20% of dose |
| INR | 1.4-1.9 | Increase by 10% of dose |
| INR | 2.0-3.0 | No change |
| INR | 3.1-4.0 | Decrease by 10% of dose |
| INR | 4.1-4.5 | Decrease by 20% of dose |
| INR | >4.5 | Hold dose, check INR daily until INR <4.5 then restart at 20% less than previous dose |

# Appendix 2: Ethical approval letters

DE MONTFORT UNIVERSITY LEICESTER

HLS FREC Ref: 1527

25th March 2015

Basma Zuheir Al-Metwali
PhD Candidate

Dear Basma,

**Re: Ethics application – Clinical evaluation of a new computerised algorithm for warfarin dosing in children after congenital heart surgery at Glenfield Hospital, Leicester. (ref: 1527)**

I am writing regarding your application for ethical approval for a research project titled to the above project. This project has been reviewed in accordance with the Operational Procedures for De Montfort University Faculty of Health and Life Sciences Research Ethics Committee. These procedures are available from the Faculty Research and Commercial Office upon your request.

I am pleased to inform you that ethical approval has been granted by Chair's Action for your application. This will be reported at the next Faculty Research Committee, which is being held on 18th June 2015.

Should there be any amendments to the research methods or persons involved with this project you must notify the Chair of the Faculty Research Ethics Committee immediately in writing. Serious or adverse events related to the conduct of the study need to be reported immediately to your Supervisor and the Chair of this Committee.

The Faculty Research Ethics Committee should be notified by e-mail to hlsfro@dmu.ac.uk when your research project has been completed.

Yours sincerely,

M. Grootveld

**Professor Martin Grootveld**
Chair
Faculty Research Ethics Committee
Faculty of Health & Life Sciences
De Montfort University

Email: hlsfro@dmu.ac.uk
Web: http://www.dmu.ac.uk/research/ethics-and-governance/faculty-specific-procedures/health-and-life-sciences-ethics-procedures.aspx

**Faculty of Health and Life Sciences,** Edith Murphy House, The Gateway, Leicester LE1 9BH.
**T:** (0116) 255 1551 **F:** (0116) 257 7135

dmu.ac.uk DE MONTFORT UNIVERSITY LEICESTER

Basma Al-Metwali <p13243032@myemail.dmu.ac.uk>

## FREC Amendments Approved (Ref: 1527)

1 message

**HLS Faculty Research Ethics Committee** <hlsfro@dmu.ac.uk> 9 July 2015 at 16:08
To: Basma Al-Metwali <p13243032@myemail.dmu.ac.uk>
Cc: Peter Rivers <privers@dmu.ac.uk>, HLS Faculty Research Ethics Committee <hlsfro@dmu.ac.uk>

Dear Basma

**RE: Ethics Application - Clinical evaluation of a new computerised algorithm for warfarin dosing in children after congenital heart surgery at Glenfield Hospital, Leicester. (Ref: 1527)**

Further to the original approval of the above named project, I can confirm that the Chair of the Faculty Research Ethics Committee has approved the amendment request submitted on 05/06/2015 . This will be reported in the next Ethics Committee meeting in October 2015. Data collection may commence immediately.

Should there be any further amendments to the research methods or persons involved with this project you must notify the Chair of the Faculty Research Ethics Committee immediately in writing. Serious or adverse events related to the conduct of the study need to be reported immediately to your Supervisor and the Chair of this Committee.

The Faculty Research Ethics Committee should be notified by e-mail to hlsfro@dmu.ac.uk when your research project has been completed.

Regards

**Tom Moore**

**Faculty Research Ethics Committee**

Faculty of Health & Life Sciences, De Montfort University

1.25 Edith Murphy House, The Gateway, Leicester, LE1 9BH

NHS
Health Research Authority
East Midlands - Nottingham 1 Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839273

16 September 2015

Dr Hussain Mulla
Glenfield Hospital
Groby Road
Leicester
LE39QP

Dear Dr Mulla,

| | |
|---|---|
| **Study title:** | **An observational study to compare model-based warfarin dosing to the traditional approach in children after congenital heart surgery at Glenfield Hospital, Leicester.** |
| **REC reference:** | **15/EM/0325** |
| **Protocol number:** | **1527** |
| **IRAS project ID:** | **171407** |

Thank you for your letter of 4th September 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 26 August 2015

**Documents received**

The documents received were as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper | | |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [indemnity certificate] | | |
| Participant consent form [Assent form-V19] | 19 | 26 August 2015 |
| Participant consent form [Consent form for parents-V19] | 19 | 26 August 2015 |
| Participant consent form [Consent form for Health Care Professionals-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS children Group 1-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS for HCP-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS children group 2-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS parents group 1-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS parents group 2-V19] | 19 | 26 August 2015 |
| Research protocol or project proposal [The warfarin study | 19 | 26 August 2015 |

| | | |
|---|---|---|
| protocol-V19] | | |

**Approved documents**

The final list of approved documentation for the study is therefore as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper | | |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [indemnity certificate] | | |
| Interview schedules or topic guides for participants [Topic guides for interviews] | | |
| IRAS Checklist XML [Checklist_07092015] | | 07 September 2015 |
| Participant consent form [Assent form-V19] | 19 | 26 August 2015 |
| Participant consent form [Consent form for parents-V19] | 19 | 26 August 2015 |
| Participant consent form [Consent form for Health Care Professionals-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS children Group 1-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS for HCP-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS children group 2-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS parents group 1-V19] | 19 | 26 August 2015 |
| Participant information sheet (PIS) [PIS parents group 2-V19] | 19 | 26 August 2015 |
| REC Application Form [REC_Form_07072015] | | 07 July 2015 |
| Research protocol or project proposal [The warfarin study protocol-V19] | 19 | 26 August 2015 |
| Summary CV for Chief Investigator (CI) [CV _HM] | | 24 March 2015 |
| Summary CV for student [CV -BM] | | 22 June 2015 |
| Summary CV for supervisor (student research) [CV _PR] | | 16 June 2015 |
| Summary, synopsis or diagram (flowchart) of protocol in non technical language [study synopsis] | 18 | 08 May 2015 |

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

| | |
|---|---|
| **15/EM/0325** | **Please quote this number on all correspondence** |

Yours sincerely,

**Rachel Nelson**
**REC Manager**

E-mail: NRESCommittee.EastMidlands-Nottingham1@nhs.net

*Copy to:* *Dr. Peter Rivers*

*Mrs. Carolyn Maloney*

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & INNOVATION

**Director:** **Professor Nigel Brunskill**

**Assistant Director:** **Dr David Hetmanski**

**Head of Research Operations:** **Carolyn Maloney**

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226
14/10/2015

Research & Innovation Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Dr Hussain Mulla
University Hospitals of Leicester,
Glenfield Hospital
Groby Road
Leicester
LE3 9QP

Dear Dr Hussain Mulla

| | |
|---|---|
| **Ref:** | **UHL 11438** |
| **Title:** | **An observational study to compare model-based warfarin dosing to the traditional approach in children after congenital heart surgery at Glenfield Hospital, Leicester.** |
| **Project Status:** | **Project Approved** |
| **End Date:** | **05/08/2016** |

**Date of Valid Application:** 14/10/2015
**Days remaining to recruit first patient:** 70 Days remaining

I am pleased to confirm that with effect from the date of this letter, the above study has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed between UHL & the Sponsor. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&D Office.

In order for the UHL Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first patient will be recruited within 70 days of receipt of a Valid Application. The date that a Valid application was received is detailed above, along with the days remaining to recruit your first patient. **It is essential that you notify the UHL Data**

**Management Team as soon as you have recruited your first patient to the study either by email to RIData@uhl-tr.nhs.uk or by phone 0116 258 4573.**

If we have not heard from you within the specified time period we will contact you not only to collect the data, but also to record any issues that may have arisen to prevent you from achieving this target. It is essential that you get in touch with us if there is likely to be a problem in achieving this target so that we can discuss potential solutions. The Trust is contractually obliged to meet the 70 day target and if an adequate reason acceptable to the NIHR has not been submitted to explain the issues preventing the recruitment of your first participant, the Trust will be financially penalised.

In addition, we are required to publish the Title, REC Reference number, local target recruitment and actual recruitment as well as 70 days data for this study on a quarterly basis on the UHL public accessed website.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

| Description | Version |
|---|---|
| REC Favourable Opinion Letter | Dated: 16 September 2015 |
| Participant consent form [Assent form-V19] | V19 Dated: 26 August 2015 |
| Participant consent form [Consent form for parents-V19] | V19 Dated: 26 August 2015 |
| Participant consent form [Consent form for Health Care Professionals-V19] | V19 Dated: 26 August 2015 |
| Participant information sheet (PIS) [PIS children Group 1-V19] | V19 Dated: 26 August 2015 |
| Participant information sheet (PIS) [PIS for HCP-V19] | V19 Dated: 26 August 2015 |
| Participant information sheet (PIS) [PIS children group 2-V19] | V19 Dated: 26 August 2015 |
| Participant information sheet (PIS) [PIS parents group 1-V19] | V19 Dated: 26 August 2015 |
| Participant information sheet (PIS) [PIS parents group 2-V19] | V19 Dated: 26 August 2015 |
| Research protocol or project proposal [The warfarin study protocol-V19] | V19 Dated: 26 August 2015 |
| Summary, synopsis or diagram (flowchart) of protocol in non technical language [study synopsis] | V18 Dated: 08 May 2015 |
| Minor Amendment 1 | REC Letter Dated: 10 September 2015 |
| Notice of Minor Amendment - To amend Protocol Sentence Part B, Section 5, Qu:13 | Dated: 04 September 2015 |

| | |
|---|---|
| UHL Pharmacy Approval | Dated: 10 August 2015 |
| MHRA N/A | Email from MHRA Dated: 22 May 2015 |
| **Staff Approved to work on this study as per approved SSI form are as follows:** | Signed Dated: 22 June 2015 |
| Hussain Mulla CV, GCP and Consent Assessment received | |
| Ms Basma Al-Metwali CV, GCP and Consent Assessment received- Honorary UHL Contract also received valid from 03 March 2014 until 03 March 2017 | |
| Dr. Peter Rivers (Role of Academic Supervisor on DMU Premises only) | |

***Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.***

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and individually.

Documents listing the roles and responsibilities for all individuals involved in research can be found on the R&I pages of the Public Website. It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting www.leicestershospitals.nhs.uk/aboutus/education-and-research

The R&I Office is keen to support and facilitate research where ever possible. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office. Our contact details are provided on the attached sheet.

We wish you every success with your research.

Yours sincerely

Carolyn Maloney

Carolyn Maloney
**Head of Research Operations**

Encs: .R&I Office Contact Information

NHS
Health Research Authority

**East Midlands - Nottingham 1 Research Ethics Committee**
Royal Standard Place
Nottingham
NG1 6FS

24 February 2016

Dr Hussain Mulla
Senior Research Pharmacist
University Hospitals of Leicester
Glenfield Hospital
Groby Road
Leicester
LE39QP

Dear Dr Mulla

| | |
|---|---|
| **Study title:** | **An observational study to compare model-based warfarin dosing to the traditional approach in children after congenital heart surgery at Glenfield Hospital, Leicester.** |
| **REC reference:** | **15/EM/0325** |
| **Protocol number:** | **1527** |
| **Amendment number:** | **Substantial Amendment 2 05/02/2016** |
| **Amendment date:** | **05 February 2016** |
| **IRAS project ID:** | **171407** |

The above amendment was reviewed on 23 February 2016 by the Sub-Committee in correspondence.

**Ethical opinion**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

**Approved documents**

The documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Notice of Substantial Amendment (non-CTIMP) | Substantial Amendment 2 05/02/2016 | 05 February 2016 |
| Other [Assent Form] | 20 | 02 February 2016 |
| Participant consent form [Consent From for Health Care Professionals] | 20 | 02 February 2016 |
| Participant consent form [Consent Form Parents] | 20 | 02 February 2016 |
| Participant information sheet (PIS) [Children Group 1] | 20 | 02 February 2016 |

| | | |
|---|---|---|
| Participant information sheet (PIS) [Children Group 2] | 20 | 02 February 2016 |
| Participant information sheet (PIS) [For HCP] | 20 | 02 February 2016 |
| Participant information sheet (PIS) [Parents Group 1] | 20 | 02 February 2016 |
| Participant information sheet (PIS) [Parents Group 2] | 20 | 02 February 2016 |
| Research protocol or project proposal | 20 | 02 February 2016 |

**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

**R&D approval**

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

**15/EM/0325: Please quote this number on all correspondence**

Yours sincerely

P.P

**Dr Carl Edwards**
**Chair**

E-mail: NRESCommittee.EastMidlands-Nottingham1@nhs.net

*Enclosures:* *List of names and professions of members who took part in the review*

*Copy to:* *Mrs. Carolyn Maloney, University Hospitals of Leicester NHS Trust*
*Dr. Peter Rivers*

**East Midlands - Nottingham 1 Research Ethics Committee**

**Attendance at Sub-Committee of the REC meeting on 23 February 2016**

**Committee Members:**

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| Dr Carl Edwards (Chair) | Investment Advisor | Yes | |
| Dr Ursula Holdsworth | Retired Staff Grade Community Paediatrician | Yes | |

**Also in attendance:**

| *Name* | *Position (or reason for attending)* |
|---|---|
| Ms Teagan Allen | REC Assistant |

# Appendix 3: Consent and assent forms

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road
Leicester
LE3 9QP

Tel: 0116 2871471
Fax: 0116 2583950
Minicom: 0116 2879852

## Consent form for parents and legal guardians

**Project Title: An observational study to compare model-based warfarin dosing to the traditional approach in children after congenital heart surgery at Glenfield Hospital, Leicester.**

**Short title: Model-based versus traditional warfarin dosing in children.**

**Study number: UHL11438**

**Patient Identification number for this trial:**

**Name of Researcher:**

**Please initial all boxes**

**1.** I confirm that I have read and understand the information sheet dated 02/02/2016 (version 20) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

**2.** I understand that my child's participation is voluntary and that I am free to withdraw my child from the study at any time without giving any reason, without my child's medical care or legal rights being affected. ☐

**3.** I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by responsible individuals from the study team, NHS Trust or from regulatory authorities where it is relevant to my child's taking part in research. I give permission for these individuals to have access to my child's records. ☐

**4.** I agree to collection of mouth swab from my child for the purpose of genetic testing for warfarin treatment. ☐

**5.** I agree to my child's NHS number being checked through information held by the NHS and the General Register Office. ☐

**6.** I agree for my child to take part in the above study. ☐

**Name of Child:** _____

| _____ | _____ | _____ |
|---|---|---|
| **Name of Parent (BLOCK LETTERS)** | **Date** | **Signature** |
| _____ | _____ | _____ |
| **Name of Person taking consent (if different from researcher) (BLOCK LETTERS)** | **Date** | **Signature** |
| _____ | _____ | _____ |
| **Researcher (BLOCK LETTERS)** | **Date** | **Signature** |

When complete, 1 copy should be given to Parents/ Legal guardians, 1 should be placed in the patients' medical notes and 1 copy should be placed in the research site file.

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road
Leicester
LE3 9QP

Tel: 0116 2871471
Fax: 0116 2583950
Minicom: 0116 2879852

## Assent form for children and young people over 12 years old

**(To be completed by the child and their parent(s)/legal guardian)**

**Project title: An observational study to compare model-based warfarin dosing to the traditional approach in children after congenital heart surgery at Glenfield Hospital, Leicester.**

**Short title: Model-based versus traditional warfarin dosing in children.**

**Name of Researcher:**

**Please tick whatever you agree with**

1. Have you read (or has someone read to you) the information about this study?

**YES** ☐ **NO** ☐

2. Has somebody (study doctor, parent/guardian) explained this study to you?

**YES** ☐ **NO** ☐

2. Do you understand what this study is about?

**YES** ☐ **NO** ☐

3. Have you asked all the questions you want?

**YES** ☐ **NO** ☐

4. Have you had your questions answered in a way you understand?

**YES** ☐ **NO** ☐

**5.** Do you understand that it is okay to stop taking part at any time?

**YES** ☐ **NO** ☐

**6.** Do you agree to collection of mouth swab for the purpose of genetic testing for warfarin treatment?

**YES** ☐ **NO** ☐

**7.** Are you happy to take part?

**YES** ☐ **NO** ☐

**Name of Child** ……..

Your parent(s) or guardian must write their name(s) here too if they are happy for you to take part in the project:

**Print name:** _____

**Sign:** _____

**Date:** _____

**Investigator's name:** _____

**Sign:** _____

**Date:** _____

When complete, 1 copy should be given to Parents/ Legal guardians, 1 should be placed in the patients' medical notes and 1 copy should be placed in the research site file

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road
Leicester
LE3 9QP

Tel: 0116 2871471
Fax: 0116 2583950
Minicom: 0116 2879852

## Consent form for Health Care Professionals

**Project Title: An observational study to compare model-based warfarin dosing to the traditional approach in children after congenital heart surgery at Glenfield Hospital, Leicester.**

**Short title: Model-based versus traditional warfarin dosing in children.**

**Study number: UHL11438**

**Participant Identification number for this trial:**

**Name of Researcher:**

**Please initial all boxes**

**1.** I confirm that I have read and understand the information sheet dated 02/02/2016 (version 20) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

**2.** I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving any reason. ☐

**3.** I agree to take part in the above study. ☐

| _____ | _____ | _____ |
|---|---|---|
| **Name of Participant (BLOCK LETTERS)** | **Date** | **Signature** |
| _____ | _____ | _____ |
| **Name of Person taking consent (If different from researcher) (BLOCK LETTERS)** | **Date** | **Signature** |
| _____ | _____ | _____ |
| **Researcher (BLOCK LETTERS)** | **Date** | **Signature** |

## Appendix 4: Rounding of Predicted warfarin doses

| Model dose (mg) | Practical dose (mg) |
|---|---|
| 0.35 – 0.64 | 0.5 |
| 0.65 – 0.79 | Alternating 0.5 and 1.0 |
| 0.8 – 0.99 | 1.0 |
| 1.0 -1.14 | 1.0 |
| 1.15 -1.34 | Alternating 1.0 and 1.5 |
| 1.35 -1.64 | 1.5 |
| 1.65 -1.79 | Alternating 1.5 and 2.0 |
| 1.8 -1.99 | 2.0 |
| 2.0 -2.14 | 2.0 |
| 2.15 -2.34 | Alternating 2.0 and 2.5 |
| 2.35 -2.64 | 2.5 |
| 2.65 -2.79 | Alternating 2.5 and 3.0 |
| 2.8 -2.99 | 3.0 |
| 3.0 -3.14 | 3.0 |
| 3.15 -3.34 | Alternating 3.0 and 3.5 |
| 3.35 -3.64 | 3.5 |
| 3.65 -3.79 | Alternating 3.5 and 4.0 |
| 3.8 -3.99 | 4.0 |
| 4.0 -4.14 | 4.0 |
| 4.15 -4.34 | Alternating 4.0 and 4.5 |
| 4.35 -4.64 | 4.5 |
| 4.65 -4.79 | Alternating 4.5 and 5.0 |
| 4.8 -4.99 | 5.0 |
| 5.0 -5.14 | 5.0 |
| 5.15 -5.34 | Alternating 5.0 and 5.5 |
| 5.35 -5.64 | 5.5 |
| 5.65 -5.79 | Alternating 5.5 and 6.0 |
| 5.8 -5.99 | 6.0 |
| 6.0 -6.14 | 6.0 |
| 6.15 -6.34 | Alternating 6.0 and 6.5 |
| 6.35 -6.64 | 6.5 |
| 6.65 -6.79 | Alternating 6.5 and 7.0 |
| 6.8 -6.99 | 7.0 |
| 7.0 -7.14 | 7.0 |
| 7.15 -7.34 | Alternating 7.0 and 7.5 |
| 7.35 -7.64 | 7.5 |
| 7.65 -7.79 | Alternating 7.5 and 8.0 |
| 7.8 -7.99 | 8.0 |
| 8.0 -8.14 | 8.0 |
| 8.15 -8.34 | Alternating 8.0 and 8.5 |
| 8.35 -8.64 | 8.5 |
| 8.65 -8.79 | Alternating 8.5 and 9.0 |

| | |
|---|---|
| 8.8 -8.99 | 9.0 |
| 9.0 -9.14 | 9.0 |
| 9.15 -9.34 | Alternating 9.0 and 9.5 |
| 9.35 -9.64 | 9.5 |
| 9.65 -9.79 | Alternating 9.5 and 10.0 |
| 9.8 -9.99 | 10.0 |
| 10.0 -10.14 | 10.0 |
| 10.15 -10.34 | Alternating 10.0 and 10.5 |
| 10.35 -10.64 | 10.5 |
| 10.65 -10.79 | Alternating 10.5 and 11.0 |
| 10.8 -10.99 | 11.0 |

## Appendix 5: Topic guides for interviews

### Topic guide (1) Group 1 participants

Hello, I'm Basma Al-Metwali. Thank you very much for agreeing to take part in my research. The purpose of our meeting is to talk about your son/daughter's warfarin therapy and how you manage it.

It's important that I get to know how it is for your son/daughter managing warfarin therapy. I imagine that this has been very new for you and that you may feel that you have been on a bit of a journey when learning about how best to manage the warfarin medication?

So, I'd like to start off by asking you to think back to when you first started warfarin therapy. How did you feel when the doctor (or nurse) first explained what warfarin therapy is, and why you need to take it?

Now that you are experienced in warfarin therapy…

Supplementary prompts (as needed):

Can you tell me about what you know about warfarin and why it is used after heart surgery?

**a.** Monitoring (why is this needed?)

**b.** How do you know whether the dose needs adjusting up or down?

**c.** How do you feel about being involved in the monitoring of warfarin therapy?

**d.** Who should take responsibility for monitoring the warfarin dose? (Doctor? Nurse? Self? parent?)

**e.** Who is responsible for getting this dose right?

**f.** How do you feel about the number of INR measurements that are required for monitoring the warfarin dose?

**g.** Overall, how do you feel about the frequency of warfarin dose changes?

**h.** Would you like to comment on other factors that, in your experience, have affected the warfarin dose and monitoring process?

Prompt: e.g. other medicines, diet, and illness.

### Topic guide (2) Group 2 participants

***[interviewer will use discretion to determine whether to omit areas that have previously been covered during the first interview]***

Hello, I'm Basma Al-Metwali. Thank you very much for agreeing to take part in my research. The purpose of our meeting is to talk about your son/daughter's warfarin therapy and how you manage it.

It's important that I get to know how it is for your son / daughter managing warfarin therapy. I imagine that this has been very new for you and that you may feel that you have been on a bit of a journey when learning about how best to manage the warfarin medication?

So, I'd like you to think back to the time when you first knew that you were to receive warfarin therapy. How did you feel when you first learned that you have been prescribed warfarin?

Can you tell me about what you know about warfarin and why it is used after heart surgery. *(note for interviewer: omit in second interview)*

Possible prompts:

**a.** Monitoring (why is this needed?)

**b.** How do you know whether the dose needs adjusting up or down?

**c.** How do you feel about being involved in the monitoring of warfarin therapy?

**d.** Who do you think is the best judge to get the dose of warfarin correct?

**e.** Based on your experience so far, how confident are you that the dose of warfarin will be correct?

**f.** How do you feel about the number of INR measurements that are required for monitoring the warfarin dose?

**g.** Overall, how do you feel about the frequency of warfarin dose changes?

**h.** Would you like to comment on other factors that, in your experience, have affected the warfarin dose and monitoring process?

Prompt: e.g. other medicines, diet, illness

**Topic guide (3) Health care professional**

Hello, I'm Basma Al-Metwali. Thank you very much for agreeing to take part in my research. The purpose of our meeting is to talk about your experience with warfarin dosing/ monitoring before and after using the new warfarin dosing model.

**1.** Setting the new warfarin dosing model on one side for a moment, could you reflect upon your overall approach to warfarin dosing.

Prompt: What are the obstacles that you usually encounter in getting and obtaining the INR within the therapeutic range?

**2.** Would you tell me about your experience of using the new warfarin dosing model?

Prompt questions:

**a.** Has the new warfarin dosing model influenced your overall approach to warfarin dosing?

Would you like to comment upon any advantages or disadvantages of using the new warfarin dosing model?

**b.** Would you recommend the new warfarin dosing model to other clinicians in similar circumstances? Please comment on your recommendation.

# Appendix 6: Coding of interviews

## 1- Families' interviews:

| | Thematic areas | | | |
|---|---|---|---|---|
| **Code** | Adherence | Managing medication/ coping mechanisms | Dose decision | Model dosing/ monitoring |
| Anxious at the beginning/ worrying | | x | | |
| Not like aspirin | x | x | | |
| Fluctuating/flexible dose | x | x | | |
| Prevents clots in the circulation | x | x | | |
| For smooth circulation | x | x | | |
| Somebody will ring and tell what to give the child | | | x | |
| Manuals/handouts/helpful/ beneficial/clear/easy to read | | x | | |
| Once a day dose is not too complicated/comfortable | x | | | |
| Routine/ habit/ at bedtime | x | | | |
| Test bothering child at beginning/ then used to it | | x | | |
| No changes in diet/balanced diet | x | x | | |
| More careful about falls | | x | | |
| Newly started warfarin/ no events of falls/ injury/ antibiotic use | | x | | |
| More careful with warfarin than with aspirin | | x | | |
| Frequency of tests (model)/ random/ not stabilised/ not bothered/ not ideal/ not a pain/ inconvenient | | | | x |
| Hospital INR testing is manageable | x | x | | |
| Doctor/ me/ pharmacist/ expert to decide the dose | | | x | |
| Similar pattern of doses (model) | | | x | x |
| Liquid form/ easy to manage | x | x | | |
| Tablet form/ easy to manage | x | x | | |
| Holidays | x | x | | |
| Future problems of periods and pregnancy | | x | | |

| | Thematic areas | | | |
|---|---|---|---|---|
| **Code** | Adherence | Managing medication/ coping mechanisms | Dose decision | Model dosing/ monitoring |
| Communication/ relationship with CLN | x | x | | |
| Get the child involved | x | x | | |
| Warnings about bruising | | x | | |
| Warfarin new for them | x | x | | |
| CLN flexible with testing times | x | x | | |
| Easier than was thought at the beginning | x | x | | |
| **Group 2 parents and teenage patient** | | | | |
| Handle warfarin better than consultants | x | x | x | |
| Parents are the best judge of dose<br>90, 99% of time right | x | x | x | |
| Information on phone call | x | x | | |
| Bruising only | | x | | |
| High INR target/ maintain it | x | x | | |
| Growth spurt | | x | x | |
| Antibiotics don't change the INR | | x | x | |
| Green vegetables/ not huge amount | x | x | x | |
| Do it naturally/ as less medicine as possible | x | | x | |
| List of medicines to avoid | x | x | | |
| Listen to what have been told/ open minded | x | x | | |
| Long list given | | x | | |
| Learn your own techniques | x | x | | |
| Home INR machine/ easier | x | x | | |
| Sensible with warfarin | x | x | | |
| Test earlier when unwell/ ring in | x | x | | |
| Never enough frequency of INR measurements | | x | | |
| No longer than a week | x | | | |
| Not ring in when in range/ only when need to | x | x | x | |

| | Thematic areas | | | |
|---|---|---|---|---|
| **Code** | Adherence | Managing medication/ coping mechanisms | Dose decision | Model dosing/ monitoring |
| Discuss with consultants | | x | x | |
| Liquid warfarin | x | x | | |
| Easily bruising | | x | | |
| Communication with consultants/ telephone/ information passed | x | x | x | |
| Frequency of testing not consistent | | | | x |
| Dosage so high/ not good dosage | | | | x |
| Person to person is better | | | | x |
| Consultant way | | | | x |
| Life implications | x | x | | |
| Risk of bleeding | x | x | | |
| Restrictions on sports | | x | | |
| Drinking (alcohol) | x | x | | |
| List of foods to avoid | x | x | | |
| Balance | | x | | |
| Test/ hurt fingers/ annoying | | x | | |
| Family support/ help | x | x | | |
| Self test/ responsible | x | x | | |
| Part of life (warfarin) | x | x | | |
| Miss checking at college | x | | | |
| Pot to remember the dose | x | x | | |
| Outside the norm/ holidays | x | x | | |
| Doctors/ best judge of dose | | | x | |
| 99% confident | x | | x | |
| Home machine/ very useful | x | x | | |
| GP surgery/ pharmacy | | x | | |
| Stable (dose changes) | x | x | | |
| Frequent dose changes/ annoying/ manageable | x | x | | |
| Tablet/ preferred/ easy/ colours | x | x | | |
| Diet/ careful | | x | | |
| Alcohol restriction | x | x | | |
| Sports restriction | | x | | |
| Cost of strips/ warfarin | x | | | |
| Part of the day | x | x | | |
| Family | x | x | | |
| Life style easier | x | | | |
| Monitoring easier | x | | | |
| Balanced/ rarely bad/ stable/ within range (INR Model phase) | | | | x |
| Dose changes not that frequent | | | | x |

## 2- Doctors' interviews

| | Thematic areas | | | |
|---|---|---|---|---|
| **Code** | Medical / Clinical knowledge | INR monitoring | Dose decision | Model dosing/ monitoring |
| Target INR range | x | | | |
| Initial dose and target INR range | x | | | |
| Indication | x | x | x | |
| Patient's condition | x | x | x | |
| Transition from heparin to warfarin | x | | | |
| Overlapping time | x | | | |
| Mechanical valves/ position of valves (aortic vs mitral) | x | x | x | |
| Fontan | x | x | x | |
| Variable target INR range | x | x | | |
| Target range sometimes changed transiently | x | x | | |
| Different INR sets for different diagnoses/ MVR, AVR Fontan | | x | | |
| Risk of bleeding | | x | x | |
| Not one size fits all | x | x | | |
| Guidelines/ individualised | x | x | x | |
| Guidelines | x | x | x | |
| Risk of internal bleeding | | x | | |
| Monitoring the INR | | x | | |
| Valves are tested more frequently than Fontan | | x | | |
| Frequent INR monitoring for mitral valve/longer intervals for Fontan patients | | x | | |
| Frequent monitoring/ intercurrent illness/ infection/ antibiotics | | x | | |
| Individual approaches | x | x | x | |
| Rate of change of INR | | x | x | |
| Significant INR changes are very concerning in MVR patients | | x | | |
| Low INRs are worrying in mitral valve patients | | x | | |
| Consistent INRs | | x | | |

| | Thematic areas | | | |
|---|---|---|---|---|
| **Code** | Medical / Clinical knowledge | INR monitoring | Dose decision | Model dosing/ monitoring |
| Indication | x | x | x | |
| How far out of range | x | | x | |
| Underdosing more problematic | | | x | |
| Caution about mechanical mitral valves | x | x | x | |
| Caution about reducing/ stopping warfarin | x | x | x | |
| Risk of hospital admission and IV heparin | | x | x | |
| Accuracy of home INR kits | x | x | | |
| Mildly out of range INRs | x | x | x | |
| Clinical picture | x | x | x | |
| More concerns about mechanical valves than Fontan | x | | | |
| Risk of thrombosis/ valve thrombosis/ death | x | x | x | |
| Risk of clotting is higher in mechanical mitral valve | x | x | x | |
| MVR in infants/ very high risk group | x | x | x | |
| Young children with small valves in the mitral position are very high risk group | x | x | x | |
| Preference to keep slightly higher INR | x | x | | |
| Dosing error even with the liquid form | x | | x | |
| Hospital admission inconvenient for patients | | x | x | |
| Personal experience in dose decision | x | | x | |
| INR instability | | x | | |
| Unpredictability in children/ difficult to control | | x | | |
| Young children/ frequent infections | | x | | |
| Compliance of teenagers | x | | | |
| Miss the dose | x | x | | |

| | **Thematic areas** | | | |
|---|---|---|---|---|
| **Code** | Medical / Clinical knowledge | INR monitoring | Dose decision | Model dosing/ monitoring |
| Adolescent patients with valves/ dosing/ miss warfarin/ alcohol | x | x | | |
| Model dosing is sensible/ rarely disagree with | | | | x |
| Disagree with model dosing in certain cases | | | | x |
| Personal experience in dose changing and INR testing interval when INR is out of range | x | | | |
| Trust in model dosing in patients without complexities | | | | x |
| Model dosing is useful in older children | | | | x |
| Model dosing is acceptable and consistent in Fontan patients | | | | x |
| Occasional disagreement with model doses in mitral valve patients | | | | x |
| Independent prescribing/no need for doctors | | | | x |
| Model doesn't take clinical picture into account | | | | x |
| Cautions about model doses in labile patients | | | | x |
| Model dosing would be faster for patients | | | | x |
| Some doctors over-treat out-of-range INRs | x | | | x |
| Combined approach for higher risk patients | | | | x |
| Modify the target INR range | | | | x |
| Need to know the study results/ more time to establish | | | | x |

### 3- Nurses' interviews

| | Thematic area | | | | |
|---|---|---|---|---|---|
| **Code** | Training/ education/ monitoring | Adherence | INR monitoring | Dose decision | Model dosing/ monitoring |
| Family education about warfarin | x | | | | |
| Family education on home INR machines if they wish to have them | x | | | | |
| Home INR testing is more convenient | x | | x | | |
| More caution with valve patients (esp mitral valve) than with Fontan | | | x | x | |
| Doctors' experience in prescribing warfarin | | | x | x | |
| Changing the dose | | | | x | |
| INR instability | | | x | | |
| Volume of phone calls | x | | | | |
| Dosing process is time consuming | x | | | | |
| Training is time consuming | x | | | | |
| Families change doses less frequently than doctors | | x | | x | |
| Fontan patients are stable | | | x | | |
| The more frequent testing the more INR fluctuations | | | x | | |
| Model working very well for some families | | | | | x |
| Model works well for stable patients (Fontans) | | | | | x |

| | Thematic area | | | | |
|---|---|---|---|---|---|
| **Code** | Training/ education/ monitoring | Adherence | INR monitoring | Dose decision | Model dosing/ monitoring |
| Model does not change dose or tell to give LMWH when INR is very low | | | | | x |
| A couple of families who did their own dosing | | x | | x | x |
| Some families questioned the model dosing | | | | | x |
| More frequent INR testing | | | | | x |
| Computer dosing did not put anybody in danger | | | | | x |
| Model dosing done in a timely manner | | | | | x |
| Missed dosing during weekends | | | | | x |
| Issue when can't get hold of parents | x | | | | |
| A handful of non-compliant families | | x | | | |
| Some families query the prescribed dose | | x | | x | |
| Majority of families who do their own dosing are right | | x | | x | |
| Teaching about warfarin | x | | | | |
| Impact on INR | | | x | | |
| Education takes a while to register | x | | | | |

| | Thematic area | | | | |
|---|---|---|---|---|---|
| **Code** | Training/ education/ monitoring | Adherence | INR monitoring | Dose decision | Model dosing/ monitoring |
| Constant ongoing education | x | | | | |
| Fontan patients are very stable | | | x | x | |
| Patients with mechanical valves are tested more frequently | | | x | | |
| Not admitting taking too much broccoli | | x | | | |
| Teenagers not admitting takin too much alcohol | | x | | | |
| Parents know their child better | | x | | | |
| No consistency in doctors' dosing | | | | x | |
| Fluctuating INRs because of changing dose | | | x | x | |
| Massive change in INR because of antibiotics | | | x | | |
| Home INR machine | x | | x | | |
| Model is very good for Fontan patients | | | | | x |
| Model not preferred for valve patients | | | | | x |
| Message left on answer phone | x | | | | |
| Need for anticoagulation nurse | x | | | | |
| Some consultants agree with parents' dosing | | x | | x | |

# Appendix 7: Transcripts of the interviews

## A- Families' interviews

### 1- Interview number 1: participant 2006's parents.

Interviewer: So..err.. Hello again…
Evan: Hello
Interviewer: errr.. I would like to introduce myself again
Bang bang bang
Interviewer: my name is Basma Al-Metwali errr.. I'm a PhD research student so doing my research on warfarin so.. er.. as you know the purpose of our meeting today is to.. errr.. talk about [child's] warfarin therapy and how you manage that.. so.. umm.. **it is** very important to me to know that umm how it is for you managing warfarin treatment for [child].. umm.. I. I imagine that this has been very new for you .. errr ..you know getting on with the warfarin treatment.. errr.. so.. and that you may feel that you have been like on a bit of journey since he..
Evan: yeah
Interviewer: ever started his warfarin treatment.
Bang bang bang
Evan: yeah.. I mean It's been OK, hasn' it? It's not.. it's.. it's..
Michelle: I say we know.. it's quite cheeky but I say **we** know how to handle [child]'s warfarin better.. than when **we** ring the consultant sometimes.. because.. we know what he is likin' himself in a day.. we know if he's had a.. ummm.. what he's had to eat.. we know if he's not feeling particularly well.. we know all of his traits…'n that can sometimes trigger tha' his INRs fluctuates or how often we should test
Interviewer: OK
Michelle: whereas the consultants differ on that opinion… they're not with him all the time
Child: aaaaaa
Evan: sh sh sh
Interviewer: so.. so yeah… so you think.. so you think that umm umm who is the best judge to get this dose correct?
Evan: it's the parents
Michelle: parents
Evan: the parents
Interviewer: aha.. so.. and.. and how confident are you that the dose.. this dose will.. will be correct?
Evan: umm..
Michelle: 90%
Evan: yeah we are..
Michelle: (at the same time) we get it right
Evan: I would say… a lot of the time the consultants would give a dosage and we would say we are not quite sure about that we'll give what we think and we'll tell you what we've give 'n I would say 99% that we're correct..
Evan: it's very rare that we are not correct, isn' it?
Michelle: yeah.. very rare
Evan: very rare that.. just like Michelle said.. because we know what he's eaten we know how much sleep he had we know how much.. if he's been.. if he's a bit under the weather.. that's really hard to get across on an answer machine sayin' it's 2.7, it's really hard to understand that which is.. which is difficult…. so I think we are we are ver..

maybe not all the parents get it bu' I think me and Michelle.. we.. really get warfarin.. I think we've.. it's just as a click with us.. we understand how it works, we understand why it works, we know… what he can and can' have, we avoid.. certain foods…. so.. we do pretty good 'n we know what's to look at for like.. bleeding gums and we didn' have any of that symptoms, have we? Not at all..
Michelle: never
Evan: but none**..** other than bruising we've had no.. of this real side effects of warfarin have we?
Michelle: and he has a really high level..
Evan: it is 4..
Michelle: it is between 3 and 4..
Interviewer: aha yeah
Michelle: so.. so the doctors **all** say.. don't be alarmed if he's bleedin' 'n his gums or nose bleed 'cause that with his level bein' quite high 'n might trigger off for no reason
Child making nosie
Michelle: never
Interviewer: Okay, so.. so according to that how do you feel that his dose needs to be adjusted?
Evan: I know..
Michelle: I don'.. think it's good for him
Evan: it it is functional for his valve we jus' had the consultant seen it as.. that's is really good for his valve to be that high we can maintain it..
Michelle: 'cause it stops any clottin'
Evan: we can maintain it.. we can maintain it that, high majority of the time.. I mean this is.. this is 2.6 today bu' we gone off off..
Michelle: (at the same time) it's when it..
Evan: the computer's diagnosis.. bu' that does'.. I don' think that it can take the fact that he jus' go' over a virus
Michelle: (at the same time with Evan) 'n the thing is as well..
Evan: so.. (at the same time) that's the thing is that's for the judgment comes in.
Michelle: I think.. that the only time we **struggle**.. with INR dosing **'an** anybody does, the consultants, we do.. the clinical liaison nurses do.. is when he has a growth spurt because it just goes from perfect to **completely** ou' of the window..
Evan: either way..
Michelle: it can go up.. it can go completely rock bottom… and then he's been on a growth spurt here before.. 'n he's been on heparin 'n it's hardly done anythin' to him (laugh)
Evan: yeah
Interviewer: (laugh) oh
Evan: yeah he's had..
Michelle: it's no' gone anywhere because his growth spurt just makin' it keep.. stay down 'n then after a' he's got over it…
Evan: because.. they.. when we attended last time with heparin..
Interviewer: yeah..
Evan: they..
Child: uhhhh
Evan: said he either had a really big growth spurt or he metabolizes medicine really quickly because.. we were having to give him a lot of heparin to even get the heparin

level up.. so it's therapeutic.. they were really struggli' there wa' a test maybe two hours.. n' like.. ev.. every six hours whatever.. to tryin' get his heparin level up… because it was jus' no' goin' up.. and they were like.. a little bi'.. what we are goin' to do… goin' 'o ge' him dalteparin injections on top of the heparin bu' … luckily they didn't need to.. and then.. the next day.. his INR was perfect, so it was like.. oh! we're going home..
Interviewer: ahahaha (laugh)
Evan: isn' it?
Interviewer: oh
Michelle: yeah.. but that's the only.. that's.. the hardest thing to manage is when they have a growth spurt… it's so hard then and because it's… the body is just doin' somethin' really random isn' it?
Evan: antibiotics..
Michelle: it's really hard..
Evan: antibiotics don't bother him.. and they normally would, they don't make a difference to [child], do they?
Michelle: no he's been on antibiotics before 'n it doesn't throw it like growth spurt does .. growth spurt is..
Evan: doesn't make any difference a bit .. you think it will go through the roof but it doesn't change it in the slightest..
Michelle: people do say.. they did say.. warn us and fore -warn us 'n it's in our paper work tha'.. if he's on antibiotics…. be careful… because it will go off but [child] like you've said 'at..
Evan: never..
Michelle: it dosen't…
Evan: it doesn' .. it's been a few times.. ear infection,
Interviewer: yeah…
Evan: water infection
Interviewer: yeah…
Evan: chest infection..
Interviewer: yeah.. yeah.. this is the other point that aaa I think you have the full experience with.. that.. you know.. with the.. what.. what things that affect the dose and the INR like.. you know.. what types of medicines..
Evan: yeah..
Interviewer: what type of diet that he has that you think it's going to affect warfarin?
Evan: yeah..
Michelle: umm
Evan: yeah.. he doesn' know we're we're really good with his diet.. I mean he.. he does have some green vegetables but.. we know he can't have a huge amounts of them he can have a little bit which is obviously.. if he didn't do tha' en' up have a poor diet… 'cause otherwise it will just be carbohydrates and carrots..
Interviewer: OK
Evan: so.. we **do** give him some green vegetables but we don't …. give him huge amounts and we tend to give him some a little bit **everyday**..
Interviewer: alright
Evan: so.. he need to have broccoli he need to have…
Child: waaaooooo
Evan: … a little bit of broccoli everyday..

Child: waaaooooo
Evan: ‘n no’ jus’ a lot one day and then none on the next, we don’ mess with it.. so we we know.. we know.. we know what is he ‘n we know if it’s really high .. for just what’s happened because high one day we know we can afford to get away with a little bi’ of garlic in the food..
Child making noise
Evan: we know it’s goin’ to bring it down but.. we know it’s no’ going to come too far down..
Michelle: we’re.. we’re trying to do it naturally, don’t we?
Evan: yeah..
Michelle: at home.. like.. we’ll say.. like him said.. if it’s really high.. we’ll go to private nursery and.. I’ll go to nursery and say to ’em… today can he have greens on his plate… because then I know naturally that’s gonna help bring it down.. ‘n at home we would go let’s have spaghetti bolognese and give him two pieces of garlic bread..
Evan: we jus’ won’t give him…
Michelle: things like that..
Evan: we a.. we a.. we adjust the INR… we adjust the warfarin ta.. what we think his diet manages… so we try to.. we wan’ to give him less.. as less medicines as possible..
Interviewer: OK
Evan: that ‘ld be the idea… but we obviously we try to get a good balance with it so.. I think as a couple we’ve got the INR… with warfarin we got it down I think..
Michelle: ummm
Evan: I think we could..
Interviewer: aha so.. aamm apart from antibiotics, aamm do you .. have.. any trouble with other medications and his INR and warfarin dose?
Evan: not this..
Michelle: he’s never been on any other medications though, has he?
Evan: even like Calpol
Michelle (at the same time): to affect it..
Evan: even like paracetamol ‘sn’t affect it I’m not sure if that would..
Michelle: no.. that’s never been.. that’s not in his book, is it? to affect it.. bu’ he’s never been on.. he hasn’ really been on any other medications since warfarin.. in the future.. he will end up on more medicines… again with his valve… whether that affects it, I don’ know..
Interviewer: so at the moment he’s just taking warfarin as a.. on a regular basis
Evan: yeah.. yeah that’s it.
Michelle: on it’s own..
Interviewer: aha.. OK.
Michelle: ‘n then a’ Calpol if he gets…
Child: peeeep peeeeep
Michelle: a little bit poorly ‘cause of.. because of the warfarin obviously he can’ have any ibuprofen products..
Evan: we know we know we know what things to avoid like.. anythin’.. any..any oth’.. any other blood thins or antiinflammatories you know..
Interviewer: have you got a list like.. um of those.. medicines?
Evan: yeah we know what he can’t have yeah we know he can’t have.. we have a list at home of what he can and can’t take so… ‘an’t take anything.. i..i.. o.. o-fen do it..

Michelle: anythin' that's got an ibuprofen.. um.. Calprofen.. Nurofen.. anythin' like tha'… ummm he can't have..
Evan: wha'.. what it comes antibiotics..
Michelle: (at the same time) at the hospital is quite good as well..
Evan: he's had lots of that.. he's got it usual..
Michelle: (at the same time) steroids.. can' have steroids..
Evan: can' have steroids.. yeah
Evan: he's had lots of different types of antibiotics, it's not jus' like amoxicillin, he's had amoxicillin, he's had.. cloxacillin and he had..
Child: peeeeep
Evan: sh sh.. another one that was err targeted for his water infection that looks so.. it isn' jus' one particular antibiotic that dosen' affect it it's jus'..
Child: peeeeeep
Evan: I don' know why..
Interviewer: OK.. so.. errr..
Child: peeeep
Interviewer: we might.. errr..
Evan: sh sh sh
Interviewer: have gone like a bit further, so I just would like to.. from you to think back to the first time when you learned that [child] is going to go on warfarin..
Evan: yeah..
Interviewer: so.. how did you feel about that? and how you managed that?
Evan: we jus' listened to what we was told..
Michelle: we're quite open-minded, aren't we?
Evan: yeah..
Michelle: so.. we've always took the approach that wha' other people say to us, we just take it on board..
Child: awawawawawaw
Michelle: so at first..
Child: aaaaawwwww
Michelle: it did seem like..
Evan: [child]..
Michelle: there was a long list of stuff tha' he could n' couldn' do.. n'..
Child: aawww
Michelle: but then when Evan n' I..
Child: aaaaaa
Michelle: actually..
Child: aaaaaaaa
Michelle: but it's like anythin'
Evan: [child]..
Michelle: if people tell you this is what you have to do on your driving license if you look at it all in the like.. uh, then actually when you ge' in the driver seat n' you do it yourself … you learn your own techniques that how to do it, don' you? so th' exactly the same as me n' Evan with warfarin, we got told the list.. until you take that list dissect it down, take i' in n' 'en process i' 'n do it yourself , we've never have a problem, have we? since day one.. we've never..
Evan: (at the same time) we were quite lucky though.. we were quite lucky that we got our own INR machine within..

Michelle: yeah
Evan: a couple of weeks..
Michelle: yeah we were so lucky..
Evan: Heart Link..
Michelle: Heart Link is amazing
Evan: so we were able to.. 'cause for the first for the first wha' was i' I be' i' was a month, wasn' i'? I was..
Michelle: back 'n forward ..
Evan: back 'n forward here.. every every three or four days..
Interviewer: ooh
Evan: 'n then one day I came in as if.. you've go' your machine..
Interviewer: ooh
Evan: so it was like.. 'n then Michelle and I came 'n were trained how to use the machine.. i' made a lo' easier have the machine a' home so we could.. we will then.. you know.. prob. we were probably test..
Michelle: without tha' machine, we would be.. **really stuck**..
Evan: yeah.. we're probably testing..
Michelle: (at the same time) 'cause we don' have a warfarin clinic where we live
Evan: (at the same time) we were probably testing too much at the start.. we were probably testing too often at the start, didn' we?.. could we be more nervous 'n anxious about.. is he in range, 's he got.. having a bad day, is i' because of the warfarin, bu'.. you soon  you soon quickly learn tha'.. in a.. it's.. it's easily managed, I think it's quite easily managed if you.. if you if you think abou' what you're doin' 'n you know the fact that it is a very strong medicine 'n it can be very.. potentially.. be very.. harmful to people you must got to be sensible with it 'n no' be like.. I mus' gonna give him loads so it shoots right upper 'an it's safe 'cause.. as its complications.
Michelle: the way tha' we work it if he wakes up once to say for example like we've phoned here and they've said righ'.. let's say for example his INR was three poin' eigh'.. 'n they say righ' for the next two da.. a four or five days.. we wan' you to give 2.5 'n 3 milligrams… alternate dose.. for tha' five day period… we woul' say okay… in **tha'** five day period.. if [child].. **appears** tha' somethin' is no' right so he migh' develop a cough or runny nose.. or he migh' 'ave got off his food… we would take it upon ourselves 'n test him earlier than that five day period..
Interviewer: OK
Michelle: 'n see what we're lookin' at.. because we're normally righ' 'n it will drop.. 'n i' so can peakin' down.. so then we know to phone 'n say actually.. we phoned early because he's not very well.. this is his dose 'n then we will be dosin'.. (couldn't be heard clearly because of the child's noise)
Child: aaaaaaaaaa (noise)
Evan: sh sh sh sh
Michelle: 'n that's how we… tend to keep on top of it, don' we?
Evan: yeah.. uh.. yeah..
Michelle: (at the same time) we jus' go' to be on the board with it, if somethin' is not the same so not because we probably more than ninety gonna be right
Interviewer: so… um.. um..
Child making noise
Evan: [child].. [child]

Interviewer: how do you think.. um.. ai.. you know.. umm.. about .. how do you feel about the.. the number of INR measurements?
Evan: what do you mean?
Interviewer: umm.. the number of INR measurements..
Michelle: oh so how frequently..
Interviewer: yeah.. mm.. the frequency of INR measurements.
Michelle: I don' think you can ever have **enough** frequency of INR measurements..
Evan: it depends, it jus' depends on how how well he is..
Michelle: because.. I.. I wouldn' trust it if somebody said to me righ'.. I want to test… I want you to test him once a week… umum (indicating no).. I wouldn' do that… I wouldn' trust it to 've sa' a week without me knowin'… what his numbers look like.. because I would potentially think hold on a minute.. if somethin' is not going righ'.. if I know he's on a s.. if we know he's on a steady bout, don't we?
Evan: um
Michelle: we'll happily do once a week
Evan: yeah
Michelle: no problem. if he starts to appear in that period of time where somethin' is not..
Evan: yeah
Michelle: quite righ', we use our own initiative, don' we?
Evan: we sometimes jus' test, 'n if he's in range, we never phone it through.. just.. a lot.. might be a lot peace of mind so if it is like a sort of seven day testi' we sort of get five days and will test 'n then if it's.. if.. there is no need to phone through 'cause he's fine, we won't phone through.. we jus' test two days later 'n phone through when we need to… 'cause sometimes.. it's jus' depends on how he it's jus' based on how [child] is
Michelle: he never really normally goes any longer than a week..
Evan: yeah
Michelle: without it needin' a variation..
Evan: yeah
Michelle: in some form
Evan: it's probably hard as he eats different..
Michelle: 'cause of his age
Interviewer: yeah
Child making noise
Evan: I think as he gets older become easier to manage, I'm guessin'.. once he stops growin', that 'll be a massive difference… 'cause that's the biggest problem
Child making noise
Interviewer: OK
Evan: 'n once he understands what he can 'n can't eat he needs to eat.. 'cause obviously his diet is massive for him… so if he's off his food or jus' dosen' want to eat that day 'cause he is too tired or whatever.. 'n then we'd have to adjust what we're givin' the following day..
Child making noise
Evan: well a lot of the time we would discuss it with the consultants.. 'n Madison will sure say OK what did you give..
Interviewer: ahha (laugh)

Evan: ‘n what’s his range.. she’s actually… I’ll let them know ‘n then come back the next day ‘n ‘n they go they go OK you were right then, we pla’ we play a little bit.. don’ we, we’re pretty good at it though, we got to say it all depends on how he feels ‘n how he’s acting..
Interviewer: yeah.. so.. and and.. um.. yeah this is for for the frequency of INRs ‘n so how how do you.. find it with the.. dose changes?
Evan: we jus’.. go with the flow.. we go.. majority of time we do what we’re told, don’ we?
Michelle: it’s fine, it’s jus’.. it doen’ affect you because… you’re doin’ the same thing regardless… all.. the only difference is one day I drop 3 one day I drop 2.5.. so there is no difference, it doesn’ affect..
Evan: yeah.. we’re on the soluble.. we only..
Interviewer: alright.. the liquid form..
Michelle: yeah
Evan: yeah.. our GP was a lo’ happy to to keep keep givin’ us that so..
Interviewer: OK
Evan: it’s.. ‘n we do fine.. that actually that’s better than the tablet form..
Michelle: umhm
Evan: ‘cause I think the tablet even we he was havin’ the tablets here..
Michelle: he was nearly sick on it
Evan: no’ only of that.. they were strugglin’ to ge’ i’ up… ‘n then.. ‘cause when we came the las’ time on heparin, they took my.. medicine off [child], the soluble.. what the umm.. it was called.. the solution one… ‘n they would givin’ him tablets ‘n it wasn’ comin’ up ‘n then Madison suggested…try givin’ him ou’ of the bottle…mm the solution.. ‘n then we wen’ home… ’cause I think.. children.. I’m not sure if this just in children, but it seems to work better… it does seem to work better than actually havin’ to like.. break off a tablet or how it work..
Michelle: it’s harder ‘n tablet, tab.. the tablet when we started here ‘n they’ve said your doctor might not let you have the liquid…
Evan: because it’s expensive..
Michelle: we need to show you how to use the tablets… so when they were showin’ us to crush them mix it with water… draw up the syringe ‘n givin’ him tha’ way... he hated it..he was nearly sick..
Interviewer: Ookay
Michelle: havin’ it, becaue.. it must be horrible ‘cause it’s pasty.. so it must be awful..
Interviewer: ooh
Michelle: whereas the liquid.. is very s.. it’s sweet in mouth..
Evan: (at the same time) it’s like Calpol..
Michelle: he’s not bothered.. ‘n that’s..
Evan: (at the same time) he’ll happily jus’ take it himself..
Michelle: so we’ve kind of got the easier route because our GP is amazin’.. ‘n he said whatever [child] needs, [child] can have..
Interviewer: Ookay
Michelle: I will prescribe it, it doesn’ bother me… so he was like liquid warfarin? yeah no problem, it might cost me.. however many hundreds of pounds a bottle… bu’.. if that’s what he needs, that’s what he’s havin’
Interviewer: alright

Michelle: so until he gets the age of sixteen.. that's the end of time 'n he'll go on tablets.. my doctor is happy to keep him on liquid warfarin until he gets the stage where to crush the tablet himself 'n take it
Interviewer: ok
Evan: I think there is too much margin for error crushin' the tablets.. I think it.. I think… if all patients have to go that route… parents, it will be difficult becau' I think there is a lo' of.. it's okay if you're goin' break half a tablet, bu' if you're goin' to start at one poin' five.. one poin' s.. one poin'.. two poin'…
Michelle: it's so hard.
Evan: we' even so.. it still a margin for error there, isn' there? cushin' tablets down 'n addin' it to water.. did you..
Michelle: (at the same time) it's less accurate.
Evan: did you ge' i' all upon syringe I can imagine that's quite difficult I think we're jus' quite lucky to have the soluble version… I'm no' sure if all GPs are just as are just as confident at givin' that out
Interviewer: yeah
Michelle: soluble warfarin definitely helps, uu liquid warfarin definitely helps
Evan: what's called now… the liquid
Michelle: liquid
Interviewer: brilliant
Michelle: it's much better.. if everyone could be given the liquid warfarin when they early on it will help so much.
Evan: so I think the tablets aa tha' he was strugglin' here, they were struggling' here to get his INR up 'n then Madison said.. try 'n give his **own** medicine at the cupboard 'n bu' then that next day he was fine.. it might 've made a combination but it di' it di' I think the children absorb it better.. I'm not a.. warfarin specialist I couldn' say how it works.. bu' I do, it does seem to work better
Interviewer: umhm.. alright, so.. anything else about his warfarin treatment and and how you manage it you would like to mention, any concerns aaa anything you might find it difficult with his umm warfarin.
Evan: the only thin' that is difficult is is that I find it difficult is the bruisin' is how **easily**.. it causes bruises.
Michelle: yeah, if he goes above four… he can literally walk past the chair, knock i', bruise..
Interviewer: yeah
Evan: yeah, he bruises **very** easily..
Michelle: it will bruise **really really** quickly.. and he can get the point where.. if he bangs, it comes up quite a bit..
Evan: he can get a quite big haematoma, was it haematoma that he can get quite quickly?
Michelle: (at the same time) mmm.. I don' know..
Evan: (at the same time) yeah, he can get a quite big haematoma
Michelle: (at the same time) mmm.. just a.. bruise.
Evan: but he's had he's had a couple of nose bleeds, hasn't he? Has he?..
Michelle: ummm..
Evan: I think it was one when he picked his nose but I think that was probably because of a different thing..
Michelle: oh yeah

Evan: ‘n it’s a.. that was sporadic that is.. we think about his finger bruise ‘cause he then came out with blood in his finger so maybe he picked his nose ‘n bleed, bu’ I don’ think he’s a nose bleed because of warfarin, has he?
Michelle: I don’t think.
Evan: in fact, that time when he cut his finger… on the gate.. it didn’ even bleed tha’ much ‘n his warfarin wasn’ quite high, was it?... ‘cause we were like oh my God ‘n woul’ take him to A ‘n E if it was really poor bu’ jus’ we held it ‘n then within a couple of seconds, it stopped.
Michelle: mm
Evan: ‘n it was like 3.5 wasn’ i.. n’ we needed to test him to make sure how… high it is.. ‘n it seems fine, so I think it’s managed very well I think,
Interviewer: okay
Evan: I don’ know if all parents are like us, I don’ know.. we’re good at it though.
Interviewer: alright ..so… thank you so much...
Evan: not at all.
Interviewer: for this valuable information..
Evan: no’ at all.
Interviewer: and for your time..
Michelle: no no that’s fine.
Evan: not at all.
Michelle: do you need to know anythin’ else? or..
Interviewer: umm.. anything that you would like to add.. aa for my questions, you have covered everything..
Evan: hahaha
Interviewer: so.. if you would like to add anything, you are more than welcome.
Michelle: no I don’, I think that’s pretty much it, just if I was to advise in the future.. things were to change, I would say tha’.. like to say young children need to be on…the liquid warfarin, that would be.. that is a massive help from start… like I’ve said at the beginning we struggled with the tablet ’n then as soon as the liquid ‘s changed, it was like.. a complete flip reversal..
Evan: (at the same time) like a new medicine..
Michelle: that never bothered us at all..
Evan: like a new medicine, wasn’ i’?
Michelle: ummm ‘n then jus’ the fact of…. I think.. it’s gonna be hard..bu’.. the communication between consultant ‘n parent ‘cause parent knows that child extremely well..
Michelle: ‘n what they’ve been doin’, ‘n have they been eatin’.. ‘n how they are in themselves.. you can… clinically see a child… I can see [child], on a telephone, they can’t see him, they can’t say what he looks like, so for them to then diagnose him a dosage.. based upon…. a potential.. of what they think, whereas if we see he’s not particulary well… we’re not a hundred percent on this because… if his warfarin level is 3.4.. bu’ then he’s turned not very well the next day… I… probably…. pu’..
Evan: mmm
Michelle: money on i’ tha’ he’s goin’ to go in the toes, it’s no’ goin’ to go the way you wan’ it to go because he’s presentin’ that.. he’s comin’ with a snuffle or somethin’ ‘n tha’ throw [child] quite significantly..
Evan: she’s .. the information tha’.. I think people well.. consultants need would be.. better.. if parents.. in other way.. were told.. when you ring up we need to know how he

is… is he eatin' well.. what's his INR, is there any signs of anythin'.. that is unwell 'cause.. 'n then make a judgment based on that because they are all facts that make massive difference to **[child]**..
Michelle: yeah
Evan: maybe not all children but to [child].. they make a **massive** difference 'n we… we then base.. our**..** what we think to give him… on that.
Interviewer: so.. do you usually.. when you ring in .. do you usually er tell the liaison nurses about..
Michelle: yeah
Interviewer: his condition..
Evan: yeah yeah
Interviewer: about if he is having like a cold.. or..
Michelle: yeah
Evan: yah, we're tellin' yah
Interviewer: changing the diet or something like that?
Evan: yeah, we.. we.. we notice everythin' like.. if we notice like blood anywhere, we would say oh he's had a nose bleed… he's had a bi' of blood in his poo.. we'd give i' all.. it's never happened thankfully… or we would say he's under the weather.. he's jus' go' over a virus.. or.. you know.. it's it's bruising really really quite a bi' at the moment, 'n we give 's much information 's we can… bu' maybe tha' always.. doesn' always ge' passed.. on to the consultants, 'cause I'm sure the liaison nurse gets right 2.7.. takes that to the consultant, he ju' goes.. you know.. issue out all these IN.. all these dosages..
Michelle: umm
Evan: she 'n can ring us again
Michelle: which is hard for the liaison nurses..
Evan: yeah, I guess..
Michelle: they have so many hundreds of… I'm sure there is so many hundreds of patients tha' ring up with their INRs dosages everyday so.. there isn' much information you can give over the phone..
Child making noise
Michelle: whether they'll be there all the day..
Evan: it's jus' more to consider than just a number I think
Michelle: I think when they're leavin' an answering message, it's kind of like.. there should be sort of .. like key factors that a' ticked in the box to say.. he's generally well.. he's generally 'n fine.. so we know tha' that dosage is gonna stay..
Child making noise
Michelle: on an equal basis..
Evan: [child]..
Michelle: 'cause 'en you're addin' more than one factor as a… a variant.. whether it's.. he's got a lo' of snuffle or he's eatin' less that day that can twitch tha' INR to change massively we notice that with him, don' we?
Evan: 'cause some parents don't, I bet a lot of parents don' understand the.. like.. what abou' vitamin K 'n how many food it's in ..
Evan: like… it's in lots of food.. 'n it's..
Michelle: they get the list, don' they?
Evan: we eat really healthy.. we don' have any processed food.. children's food.. they add lots of vitamins in.. so they're no' readin' the box 'n it says with vitamin K or added this or added that.. A,A (to the child).. 'n then.. the parents won't know 'n they

go wrong ‘n the child eats a plate full of his food that is full of vitamin K ‘n it’s gonna mess with warfarin.

**2- Interview number 2: participant 20010 and his mother.**

Interviewer: so.. umm.. hello again..
Grace: Hi.
John: Hi.
Interviewer: err.. I’d like to introduce myself, my name is Basma Al-Metwali.. err.. I’m a PhD research student doing my research on warfarin.. umm.. as you know the purpose of our meeting is.. to.. err talk about Johns’ warfarin..
John: yeah
Interviewer: treatment and.. how you manage it.. umm.. it is important that I get to know how it is for you as a.. as a parent and how for John managing warfarin treatment.. err.. I imagine that this has been very new for you..
John: yeah
Interviewer: and… that you may feel that you have been like.. on a bit of journey..
Grace: umhm.
Interviewer: with warfarin..
John: yeah.. yeah.. I suppose.. yeah
Interviewer: okay
John: can’t wait to describe it.. yeah
Interviewer: aha, so.. umm.. first I’d like you to think back to the time first .. John was prescribed warfarin..
Grace: mm
Interviewer: umm.. could you please tell me and John of course.. um.. how you felt when first knew that John is going to receive warfarin?
Grace: um.. well can say because of the life implications ‘cause he ‘as to have i’ ‘n tha’s tha’ bi’ you know.. on things… like health ‘n.. you know.. risk of bleeding.. ‘n the restriction he was goin’ to have on him havin’ sports at school..
Grace: ‘n things.. I know they found alternatives but it’s all that.. ‘n then obviously when he came to teenages… ’n his.. peers are drinkin’ ‘n John can’t .. can’t drink really..
Interviewer: aha
Grace: so.. which I know it’s probably minor ‘n everything, but you’re jus’ tryin’.. you know.. that’s..
Interviewer: okay
Grace: yeah.. that was probably the concern
Interviewer: so..so.. right at the beginning of.. of prescribing warfarin.. errr.. did you have.. like any issues with the medicine itself.. right at the beginning of treatment?
John: no.. no.. not that**..** remember? do you remember any?
Grace: no.. we jus’..
John: no
Grace: we were given a list of the foods..
John: yeah
Grace: to avoid.. ‘n.. you know it’s the balance, isn’ it? So.. he has the vitamin K vegetables.. bu’ he has them on regular basis.. so he will have broccoli ‘cause he likes it..
Grace: but he doesn’t have an excessive amount.

Interviewer: umhm.. so did you find it easy to follow that list of.. of..
Grace: yeah
John: yeah
Grace: yeah
Interviewer: of medicines.. you know.. to avoid and.. err..
John: umhm
Interviewer: umm and food and stuff like that?
John: yeah
Grace: yeah yeah yeah, pretty much.. we just.. we avoid.. we would avoid anythin' if I buy anythin' with cranberries 'n yet John
John: yeah
Grace: jus' doesn' have it..
Grace: yeah.. no that's fine.
Interviewer: okay.. so.. could you please ummm.. err… talk to me about what you know about warfarin and why it's prescribed after heart surgery?
John: uumm.. so… warfarin thins thins your blood, doesn' it?..
John: that's the purpose of it, so.. after I had heart surgery with my mechanical valve I'm not… exactly sure that you know more about it than I do, bu'.. I know.. like.. if.. my blood.. isn'… uumm… wha' is.. if it's not thin enough.. then it can clot.. is that the right thing?
John: so.. yeah… so.. I jus' need to take it to make sure that it is enough, but I can't take it.. in excessive amount so I can' overdose myself, because… I'm not sure.. what happens.. is it ae…
Grace: you can.. stroke.. (low voice)
John: stroke..
Grace: what you mean a' extreme so it may help it to..
John: yeah.. yeah..
Grace: it can bleed.. internally..
John: yeah.. bleed internally.. that's what I thought..
Grace: it can have blood in your wei, blood in your poo..
John: yeah..
Interviewer: aha.. so… errrrr.. er.. so that's why you were advised to do the monitoring?
John: yeah
Interviewer: so.. umm could you please…um.. talk about the monitoring?
John: the.. the monitoring is like err I would.. I'd like to say tha' I do i' every …. every time get it all done but it's…. I've got used to it like.. when I've started, I remember I used to hurt my fingers..
John: I remember that.. 'n then it's annoyin' when I don' bleed.. enough sometimes also..
Interviewer: so.. was it you who who.. used to do the INR right from the beginning?.. or your parents were helping you?
John: err.. right from the beginning when I was here, I remember… my dad used to help me.. my mum .. used to help me as well do i' 'n then I eventually jus' …. got err..
Grace: mmm Madison told..
John: (at the same time) I know how to do it..
Grace: John 'n me so that he…. would manage his own condition, which is better
Interviewer: aha, so do you .. you find that.. umm.. he is the best to do that?
John: yeah..

Grace: yeah..
John: yeah..
Grace: yeah.. yeah
Interviewer: okay..
Grace: yeah.. he's now
Interviewer: so.. umm.. how do you know that er your dose needs to be adjusted up or down?
John: err depending on how… far my INRs .. how far it is.. so if it's like er.. if it's too low for example.. one poin'… let's say.. one poin' seven or something, then… like the dose will.. wou' i' go up or would i' go down I'm no'…
Grace: it would increase it..
John: it will increase, yeah.. so… I'm like… also.. I have to have an injection just in case it goes to far down to bring it back up again.. if it..
Grace: dalteparin..
John: yeah.. yeah.. that's it
Grace: on on occasions when it's got.. you haven't had that for a long..
John: no no tha' was at school..
Grace: when at school.
John: yeah..
Interviewer: so.. you have been controlled?
John: yeah..
Interviewer: well controlled over the.. you know.. the past period of time?
John: yeah yeah
Grace: it's normally pretty stable now, isn' i'?
John: yeah
John: normally.
Interviewer: so.. how ..do you feel.. err.. as being involved in the monitoring of.. of warfarin?
John: I.. I don' mind i' I suppose it's jus' become.. part of my life.. really.. so.. like.. I have to do it.. carry on with it.. so..
Interviewer: aha
John: so so it's it's like.. I guess eatin' now for me…. It's jus' .. I'm used to it.. so .. yeah that's fine.
Interviewer: and err.. and Grace?
Grace: yeah yeah that's fine.. yeah we jus' get used to it.. it's jus' makin' sure.. sometimes….if.. I think the worst thing is if you're a bit later but he's been a teenager, you've got to go to college 'n you perhaps miss checkin' it on that day
John: yeah
Interviewer: umhm
Grace: that's the only thing that is important to do on the same day.. bu'.. he's been he's .. you've been quite stable for quite a while now he's been checkin' every two weeks..
Interviewer: OK, so.. so.. is it you who remind him? or he rem.. remembers that
Grace: yeah
Interviewer: from himself
Grace: yeah yeah
Interviewer: to do that?
John: yeah yeah

Grace: yeah yeah, it's it's .. yeah, we normally double check it with him tha' we're tryin' get him to.. to be responsible.. but obviously, we still there so.. it's easy.. 'n like we're takin' warfarin, we pu' that in a little pot, don't we?
John: yeah yeah yeah
Grace: for the week so…
John: so..
Interviewer: umhm
Grace: it's it makes easy to remember takin' i'
Interviewer: so..umm.. umm.. could you um.. um please explain more?
Grace: um you know.. you can get the little.. um.. you can buy the pots.. with the.. they've got Monday Tue.. the pill.. I can' think what they're called
John: they got Monday to Sunday..
Grace: they got like..
John: yeah they go' like err..
Grace: they're almost like the blister packs, bu'.. bu' you buy the pot yourself ..
Interviewer: aha
Grace: 'n you jus' dispense it for every day what you know the dose is gonna be..
Interviewer: aha
Grace: John normally gets his for every two weeks which is four poin' five 'n five so we jus' pull them ou' occasionally accordingly
Interviewer: aha
Grace: 'n jus' to try 'n give us a reminder to.. most of the time… he do remember..
John: yeah
Grace: it's when we do something 'at's.. outside the norm you know if we go out or something rather than.. because normally he take it a' home with his meal..
Grace: so it's if it's.. you know.. when he do something different.. jus' that, it's okay so I.. it's fine with tha'.. yeah
Grace: it's no' a problem
Interviewer: okay…umm.. so..err.. regarding umm the the warfarin dose, who do you think is the best judge.. to get this dose correct?
Grace: umm.. well.. the doctors
Grace: I.. I presume.. yeah.. (laughs) I assume.. well.. the bi'.. yeah.. I mean they're the ones tha' do it.. they seem to know..
John: yeah, I'ld agree
Grace: ah.. he.. I can' remember when it was, bu' ai.. ages ago we have queried it with them when we thought… I think it's probably dropped.. I can' remember it slightly 'n they've increased it quite rapidly.. 'n we.. we queried it with them..
Grace: because… because when you man'.. when you have the conditions.. I know I haven' bu' John has.. you do get used to… you know managin', however, from a safety poin' of view.. the doctors are always the best to dose it..
Grace: yeah.. yeah
Interviewer: so.. okay… and how confident are you that the dose will be correct?.. based on your experience so far?
Grace: I'ld say..
John: very confident..
Grace: very confident yeah
John: yeah
Interviewer: very confident in..

Grace: ninety nine percent..
John: yeah
Interviewer: in doctors' dose?
Grace: yeah
John: yeah
Interviewer: okay
John: nothin' 's gone wrong… apart from like.. there was only one time really which you said.. where like..
Grace: 'at's about two years ago..
John: yeah that was two years ago.. so.. so yeah.. when when it's been like err.. I 'n know.. was it two or something, 'n they've told me to take like…as on like three 'n somebody told me to take five..
Grace: yeah
Grace: they are very competent 'n then yeah.. they seem very good, yeah.
John: yeah.
John: bu' tha' was long time ago.
Interviewer: OK.. so.. umm.. how about the frequency of INR measurements? How do you feel about that?
John: ffffuuuuu… yeah.. I'm fine with that.. yeah.. suppose.
Grace: we're lucky he's got a machine..
John: (at the same time) yeah
Grace: to do it on rather than have…
John: yeah, have to come in.
Interviewer: so.. errr… yeah, do you do the INRs.. you know.. more regularly? How often do you do that?
John: aaammm.. I do.. well at the moment, I'm doin' i' every two weeks..
John: because I.. it's been stable, so it's normally.. I always.. whenever I miss a dose, I always.. umm.. do my INR to see what the outcome is.. 'n like.. if it's.. fine then.. I jus' carry on 'n call.. call i' in when.. when I actually need to, bu' if it's like.. bad..
John: then I'll.. call i' in.. the day that tested, so.. bu'.. yeah I'm fine with that.
Interviewer: so do you find the the machine.. err.. very useful?
John: yeah, I do find i' very useful, it's a lot better than.. havin' to.. have to go to hospital every like.. week or two weeks..
Grace: yeah (at the same time)
John: (at the same time) just to.. check up saves a lot of money as well..
John: so.. yeah.
Interviewer: umhm.. so.. was the machine with you right from the beginning?
Grace: yeah
John: yeah
Grace: yeah
Interviewer: so.. how often… did you.. err.. used to measure the INRs right at the beginning of treatment before he.. he.. was..
Grace: it was abou'..
Interviewer: getting stable?
Grace: daily to start off with..
Interviewer: aha.. that's right at the beginning..
Grace: yeah
Interviewer: and then afterwards?

Grace: yeah then it probably.. went to.. abou' every three days.. 'n then a week..
Interviewer: OK.
Grace: yeah.
Interviewer: and how about the dose changes? ..Umm.. do you find it.. how do you find it?
John: uummm.. yeah, I'm fine with i' normally.. like.. 'n that's jus' like.. somethin' drastic, I suppose like..
Grace: yeah
John: like.. bu'.. nothin'.
Grace: we luckily we live quite close to the GP surgeries they normally will help us say.. you know.. aa.. ah.. I'm quite.. organised with making sure he's got enough medication..
Grace: bu' the pharmacy is righ' next door to us as well.. 'n.. so they know John as well so.. 'n the GP surgery.. so it's always..
Grace: we've been quite lucky there..
Grace: so they will always get.. you know.. they get the stuff in quite urgently so..
Grace: bu' it is good.. I mean we even had an incident where we were in Spain..
John: yeah
Grace: 'n the chip was missin' out of the the strips..
Grace: so he couldn't use them.. so i' so i'..
Interviewer: Oh
Grace: we had to buy them.. bu'..umm.. bu' the pharmacist in Spain.. they got them delivered.. you know.. by the end of the day that day.. they were really really good, really helpful.. jus' took everythin', so.. it's good
Interviewer: yeah.. yeah… and umm yeah the dose changing.. umm.. I could.. umm.. the.. how often did you have like.. those dose changes? Did you have like.. a frequent dose changes or..
John: errr
Interviewer: it's OK?
John: no'.. no'.. at the start… a lo' of the time, bu'.. righ'.. for the the past year.. no, it's been around from 5 to the lowest of probably say 4..
John: and.. it.. it's really stable at the moment.
Interviewer: so..
Grace: for the past.. about three months, it's been 4.5 'n 5 alternate days so it's it's..
Interviewer: so how was it for you.. right at the beginning when there was frequent dose changing, was it easily manageable?
Grace: yeah
John: yeah, it was manageable I guess it was a bi' annoyin', bu'..
Grace: it was fine, jus' accept that that's what we had to do.. 'n that's fine.. 'n I'm like..
Interviewer: sorry?
Grace: we just accepted that that's what we had to do..
Interviewer: aha, OK.
Grace: 'n we were OK with the tablets 'n everything.. umm
Interviewer: OK, so which form of of warfarin.. is umm.. John using? Is it the tablet or the..
John: tablet.
Interviewer: tablet, right from the beginning?
John: yeah, right from the beginning.

Interviewer: aha, so.. could you.. were you find it.. umm did you find it easy to use?
John: yeah yeah yeah it's easy , I jus' pop it in my mouth 'n let them down..
John: also I don' need use water.. I jus'.. never have done, have I?
Interviewer: you never crushed the tablet?
John: no, I don't, I jus'..
Interviewer: just..
Grace: no, this is (laugh)
Interviewer: (laugh)
Grace: it's it's always.. he had to take tablet from being quite little.. well.. I know they used to give him.. an.. I mean because we have to give him the the.. the suspension when he was baby.. 'n I think he was on that many 'cause he was on diuretics as well..
Grace: 'n tha'.. he jus' began to hate them, so as soon as he was big enough to take tablets.. it was always.. prefer tablets anyway..
Grace: even with antibiotics...you know.. if he needed them.. he would rather have the tablets, it's jus' prefers them to the**..**(laugh)
Grace: so he'd never had to crush the mix, it quite swallows.. it's quite easy.
John: it's jus' easy to get them over 'n done we really jus' need put them in 'n 'en it's done.
Grace: yeah that's fine.
Interviewer: OK.. yeah.
Grace: 'n I think with warfarin as well.. I mean.. I think the fact that there are different.. the colors as well, I think tha' helps.. people with the dose.. as well.
Interviewer: umhm, so, yeah the one and the.. not point five milligrams
Grace: (at the same time) yeah yeah yeah
Interviewer: so you don't have that.. problem with.. different err.. strengths of tablets?
John: no.
Interviewer: just take the dose as it is?
John: yeah, I jus' take it.. as it is
Grace: umm
John: I never have to crush them, never have to.. put them in a liquid or somethin'..
Grace: no, jus' takes them.
John: yeah, jus' take them.
Interviewer: aha.. OK.. so.. ummm.. I would like you to comment on on some.. other things that in your experience have affected warfarin treatment.. like.. umm diet.. like.. medicines anything that you think..
John: uummm well.. there there's couple of.. so I guess my diet ss.. has to be.. always has to be.. like I have to make sure I'm careful for wha' I ea' for example when I went to Peterborough hospital.. umm they gave me a full plate of broccoli.. did'n they so..
Interviewer: (laughs)
Grace: yes.. it's alright (laugh)
John: yeah.. and..
Interviewer: did they know that you were on warfarin?
Grace: yeah (laughs)
John: yeah, they gave it as well so..
Interviewer: oh!
Grace: (laughs) yeah
Interviewer: and they gave you that big plate of broccoli?
John: yeah

Interviewer: oh!
Grace: never mind.
John: so… errr.. also with like drinks I'm not allowed to.. or.. I don'.. I do drink a bi' of alcohol bu' no' enough to make me… you know..
Grace: no.. quite awake isn' i' 'n it's at home..
John: (at the same time) yeah yeah.. it's a' home.. so.. I know they go.. well.. I'm no' old enough to go out drinkin' yet.. bu' I'm sure…I will always be the one carryin' my friends home.. so that'll be alright.
Grace: laughs.. also saves lots of money John.
Interviewer: laughs.. so do you find this.. like.. annoying?
John: no..to be.. to be honest, if.. you.. look at i' at this perspective of money wise… umm.. I think it's.. no, I'll save a lo' of money.. with.. I suppose sports.. aemm.. used to love s.. do sports a lo' than I..
Grace: yeah.
John: yeah.
Grace: you still can.
John: I still do sports.. like bu' I've always got to be more careful now..
John: yeah, bu'.. ummm.. tha's abou' it really.. like.. yeah.
Grace: yeah, I mean he's very mu' he tends to ge' paitballin' 'n things with him and I'm a little bi' more concerned..
John: mum..
Grace: 'n
John: yeah
Grace: 'n.. because tha' they can bruise quite easily with tha'..
Interviewer: aha
Grace: 'n this since did i' 'n they 've got.. 'n they 've no' on warfarin 'n they go' **huge** bruises.
Grace: bu' you kn' that's e' pace.
Interviewer: okay.. so.. have you ha.. did you have any bruises at all?
Grace: no, he didn't go.. he d.. you mean normally?
Interviewer: normally?
John: normally.. ummm..
Grace: no' really.
John: no, I never really have... I can guess at the start when I used to have.. blood tests 'n injections like.. used to get a massive bruise..
Grace: yeah
John: yeah, bu'..
Grace: that's from the needle (laugh)
John: that's from the needle.
Interviewer: aha (laugh).
John: so..yeah.
Interviewer: OK.
John: so I.. I guess maybe when I'm fallin' over bu' every body gets bruises they fall over bu'.. yeah.
Interviewer: aha.. so.. yeah.. other other types, have you had other types of bleed like a nose bleed or..
John: ummm.. I don't.. normally get nose bleeds..
John: I never really have done.. aaammm tryin' to fit aaammm

Grace: do you remember that time when you cu' your finger in Spain?
John: ah yeah on holiday..
Interviewer: oh!
John: I was bein'.. I was tryin' to make some food and.. I sort of .. was bein' stupid 'n I got the knive 'n I pu'..
John: I put it put it straight through my finger..
John: 'n so that bled quite a bi'.
Interviewer: Oh
Grace: (laughs) that was quite difficult to control.
Interviewer: Oh, so, did it take long to heal?
John: errr.. it took abou'.. probably say two three weeks.
Grace: yeah, it stopped bleedin' by the end of the night, haven' it?
John: (at the same time) stopped stopped..
Grace: Bu' it's kept starting 'n I double stripped it.
John: (at the same time) it bled for abou'.. half an hour
Interviewer: aha, half an hour?
John: yeah, so no' no' tha' long.. like I thought.. that it can be..
Grace: (at the same time) until he got some steri-strips..
John: (at the same time) 'n then I.. 'n then I did tha'.. with my finger..
John: yeah, 'n clean it a lot.
Interviewer: alright
Grace: that's OK.
Interviewer: OK.
John: I got a scar now to..
Interviewer: umhm. So.. errr.. umm.. overall, do you have any concerns about.. warfarin treatment as a medication.. err.. as monitoring.. anything that.. err.. you may concern about that?
Grace: no, er I think the only.. concern I think I mentioned this.. eh.. to you is not really a concern about the medication other than the fact.. umm.. he's got a congenital disease.. he has to have medication.. and yet the act is so ou' of date with the government, it's from 1966 or something..
Grace: 'n it doesn't recognize… um warfarin as… one of the medications, you know whereas diabetics can have their insulin 'n things, so he's gonna have to pay for it, bu' that's fine we'll help him when he's young bu' I still find that.. quite..
John: **disgusting**.. that's the word.
Grace: (laugh)
Interviewer: (laugh)
John: (at the same time) jus' disgusting people.
Grace: it's not that I object payin' i' bu' I know that warfarin is one of the cheape' drugs on the marke'.. I know the strips aren', bu'..
Interviewer: yeah
Grace: you know, 'n I know.. umm because he's in full time education.. so I think.. the pharmacy was sayin' tha' we can fill out a form for him 'n tha' was sorted for now anyway..
Grace: umm.. bu' **it is** somethin' that he will have to pay.. for.. lifelong.. bu' that's..
Interviewer: okay, so.. have you discussed ..those concerns with anyone? Like your GP..
Grace: um..
Interviewer: or maybe… the nurses.

Grace: yeah, yeah.. nothing' (laugh).. I think.. I think the um British Heart Foundation 'av appealed it 'n I've written a letter.. 'n.. no (laugh)
Interviewer: okay
Grace: (laugh) never mind
Interviewer: OK.
Grace: never mind.. that's fine, we can afford to pay for it, it's jus'.. like it's a concern like you know he's.. he's lucky he's go'.. his family tha' will hel' him find the money bu' I jus'.. concerns me (laugh) that's for those people that aren't you know..
Interviewer: OK.
Grace: anyway, bu' no.. for him, no, it's fine it's easy to take..
Grace: we know how to take it, we.. you know.. we keep on cope with.. we don't.. keep too much in stockin' 'cause we know it goes ou' of date which at the date blabla
Grace: it's fine, it's easy 'n i'?
John: yeah yeah yeah
Grace: any queries with any.. other medications..
Interviewer: yeah
Grace: interactions sometimes, we jus' check it with the pharmacist..
Interviewer: aha, so do you have a list of medications that.. umm.. umm.. like to avoid or to take care about..
John: umm
Interviewer: the INR monitoring during that time?
Grace: err.. no anti-inflammatory is no'….ummm…no… I mean like he he gets migraines occasionally, so..
Grace: we spoke to the pharmacist abou' tha' 'cause he.. i' was pre.. I tend to go to the doctors 'n get it prescribed for him anyway so..
Interviewer: OK.
Grace: yeah
Interviewer: and the doctor is aware that he is on warfarin?
Grace: yeah
John: umhm
Interviewer: OK, did you have any other troubles like.. umm.. maybe when like on antibiotics or something and you had some troubles with warfarin?
John: no.. I've never had.. any troubles with warfarin.. the only thin' I've had troubles with is penicillin.. I've got allergic to that..
John: yeah so..
John: bu' my dad is allergic to it as well..
Interviewer: oh
John: yeah.
Interviewer: OK
John: bu'.. tha's the only thing I've ever been allergic to 'n have a problem with.
John: never had a problem with warfarin**,** I.. didn' I used to say go' lisinopril.. as well..
John: back.. back when I.. was to start takin' warfarin.
Grace: they've stopped tha' now.
John: yeah tha' stopped.
Interviewer: umhm, so at the moment you are just on warfarin?
John: I'm jus' only on warfarin yeah.
Interviewer: aha. So.. umm.. John.. umm.. could you please let me know how do you feel.. or how do you see yourself with warfarin in the future?

John: uummm.. I guess because I'm used to it now I'll jus' be used to it in the future 'n… yeah.. like.. jus'… it's jus' part of my day so.. it's jus' part of my life.. it's.. it's.. like.. so.. like havin' breakfast in the morning even though I don' do that all the time.. do I?
Grace:(laugh)
Interviewer: (laugh)
John: uumm…. Yeah.. I can see it jus'.. if I ever have trouble, then I know I've always… **go'**.. my family..
Interviewer: alright
John: tha'.. you'll always be here for me no matter what..
Grace:mmm
John: yeah…. bu' yeah, I don't have.. I don't see myself in the future struggling with warfarin.. at all.
Grace: well at the long term implications for takin' a drug like warfarin though.. do they know.. or .. you know affectin' so healthwise you know like bleedin'..
Grace: or anythin'
Interviewer: okay. So as long as it is like err.. well controlled..
Grace: OK.
Interviewer: umm.. so.. I think now you are the experts..
Grace: yeah.
Interviewer: you've been like err.. around five years?
Grace: yeah.
John: yeah.
Interviewer: with it?
Grace: yeah.
Interviewer: so now you are the experts..
Grace: OK.
Interviewer: with managing it.
Grace: yeah yeah yeah.
Interviewer: so..
Grace: yeah yeah, that's true, yeah we have adjusted to it**.**
Interviewer: alright, any other comments you would like to add?
John: there will probably be something in a minute, so we'd better think now..
Grace: (laughs)
Interviewer: OK (laughs)
John: there is always, there is always something err jus' like what happen' in my job in few…. (couldn't be heard clearly because of the laughs).
Grace: (laughs)
John: so there will be something.. so.. errr….. do you think of anything right now?
Grace: no.
John: ummm…
Interviewer: please think carefully.
John: OK, errr… with warfarin like.... if.. say… for example there is a drug in America which also.. is of like.. warfarin, what it's called, do you remember what it's called?
Grace: no, bu' think they use it for people with AF maybe..
John: (at the same time) oh
Grace: here I don' think they use it for complex medical conditions.
John: I 'on' know. Bu' errr…

Grace: yes, different name ‘n i’?
John: like.. as the future change I suppose…
Interviewer: umhm
John: will warfarin ever change in a way like.. ummm…. I’m not su’, I’m not su’.. well I gue’ guess will.. it be easier like…. I can’t.. I’m not really sure wha’..
Grace: what you mean would.. would it ever be… replaced for another tablet..
John: (at the same time) yeah yeah yeah, that’s that’s..
Grace: (at the same time) that you can..
John: I can take..
Grace: not affect… other.. your other… (laughs)
John: well.. I mean make my life style easier so..
John: yeah, that’s.. so..
Interviewer: OK… do you mean regarding monitoring and the doses and all those stuff?
John: yeah yeah that sort of stuff.
John: like.. I’m used to it, bu’ I mean there is always a way….
Grace: I think.. well isn’t warfarin supposed to be the.. one of the best ones
John: (at the same time) yeah
Grace: for doin’ it though isn’ it?
Interviewer: yeah. So have you ever discussed those concerns with with a doctor like changing it to another.. medication?
John: yeah.
Grace: yeah, they don’t..
John: (at the same time) me..
Grace: (laugh) they don’t they don’t want to that I don’t know why, perhaps it’s… it’s fine.
John: yeah.. yeah, that’s.. that’s all I have.. to think about at the moment.. I suppose as technology will.. enhance..umm..
Interviewer: yeah.
John: advance.. so..
Interviewer: yeah, of course.
John: so.. things will improve.. I’m sure in about.. err.. 30 years, surgery will be easier…there’ll be more.. like.. I guess.. there might be a different think of the INR machine..
Interviewer: umhm.
John: like.. easier.. maybe jus’ you have to put your finger there ‘n scan i’ I don’ know like temperature or something.
Interviewer: alright.
John: yeah.

**3- Interview number 8: Participant 1003’s mother**

INTERVIEWER: umm… hello.. err I’m Basma Al-Metwali.. err I’m a p’ PhD student doing my research on err.. warfarin er thank you very much for agreeing to take part in my research .. umm the purpose of our meeting is to talk about [child]’s warfarin.. therapy and how you manage that.. umm it is important for me that I get to know.. err how it is for you.. err managing warfarin therapy for [child].. ummm I imagine that thi’.. this has been very new for you..
SONYA: yes.

INTERVIEWER: and errr you may feel that it has been like a b'.. you have been on a bit of journey..
SONYA: ya.
INTERVIEWER: since you.. err since [child] first started.. er warfarin.. therapy. So first I would like to start off by.. umm.. err asking you to get back to the first time when you first knew that.. er [child] is going to start.. err warfarin how did you feel when the doctor maybe the nurse ummm has told you about that?
SONYA: umm I was a bi' anxious because I know it takes a bit more… um care or attention than the aspirin tha' she was on.
INTERVIEWER: umhm.
SONYA: umm…… I fe' I felt a bi' like I didn' really know… what was to come.. whereas with the aspirin 'cause she doing on i' for so long..
INTERVIEWER: umhm.
SONYA: we knew what to expect.
INTERVIEWER: so.. errrrm.. er could you please let me know what.. what you know about warfarin and why it is required after surgery?
SONYA: errrrm it helps to.. thin the blood? as far as I'm aware.. to help stop… blood clots.. in [child]'s circulation.
INTERVIEWER: and errr why do you think um this monitoring.. this INR monitoring is required?
SONYA: Oh to make sure that umm.. it's not too thin.. or not too thick so it's at the right... consistency I suppose.
INTERVIEWER: O' OK so umm how do you know that um this dose needs to bee.. adjusted up or down?
SONYA: how do I know?
INTERVIEWER: yeah.
SONYA: so when?..
INTERVIEWER: this..
SONYA: what do you mean?
INTERVIEWER: this warfarin dose..
SONYA: yeah.
INTERVIEWER: how do you know this warfarin.. er warfarin dose..
SONYA: so if her INR.. INR 's too high.. then her dose is lower.
INTERVIEWER: OK.
SONYA: an' then if her.. INR is too low the dose is higher (laugh).
INTERVIEWER: (laugh) Oh..
SONYA: but.. somebody will ring me and tell me.. what to give her.
INTERVIEWER: OK soo.. er how do you feel about being involved in this process of monitoring?
SONYA: alright (laugh).. I suppose.
INTERVIEWER: how do you get with that?
SONYA: umm.. it's alright.. it's a bi'.. it's a bi' very new since 'cause start to g' come to the hospital.. for… her INR tests.. so sometimes… will go.. two weeks.. an' then sometimes we've been in.. places where it's been every other day..
SONYA: umm…. bu' tha' was jus' because they haven' go' the… machines for us to have a' home ye'.
INTERVIEWER: yeah.

SONYA: bu' the actual…. umm.. the actual INR tests.. she is getting' used to them so they're no'..
INTERVIEWER: not bothering her?
SONYA: they bother her bu' no' as much as they did… to begin with.
INTERVIEWER: umhm.. so.. when you first started.. err let's start right from the beginning.. err I imagine that you have been given like errrmm a set of information maybe..
SONYA: yes.
INTERVIEWER: how did you find that?
SONYA: errrrrm I found i' quite helpful… because there was a lo' of things.. abou' the warfarin tha' I didn' really know.
INTERVIEWER: umhm.
SONYA: ummm and… i' also helped to have tha' information because she started school this year so i' helped.. with having something written to pass on..
INTERVIEWER: aha.
SONYA: umm to school so they can see i'…..umm.. bu' yeah i' filled.. filled a few gaps in.. for us… once would sat an' read i' because nobody really.. on the ward.. when.. before we go to home.. nobody actually really sat with us an'.. properly explained… the warfarin.
INTERVIEWER: so who was the person..
SONYA: so..
INTERVIEWER: who explained that to you.. and gave you the handouts?
SONYA: I don' think anybody has actually properly explained it to us bu' we've read the handouts an'..
INTERVIEWER: umhm so who gave you the handouts?
SONYA: ummm… one of the nurses on the ward.. I can't remember which one it was.
INTERVIEWER: OK. And then.. then you.. after you went home that you got those.. ummm… went through them?
SONYA: ye.
INTERVIEWER: errrmm were they ea'.. those.. that information was it easy to.. like err..
SONYA: understand?
INTERVIEWER: yeah.
SONYA: yeah.. yeah yeah yeah.
INTERVIEWER: and to go on.. you know to apply it you know with erm.. her daily..
SONYA: yeah.
INTERVIEWER: you know..
SONYA: yeah.
INTERVIEWER: activities or daily life?
SONYA: there is no' tha'.. many things.. really.. tha' we.. can an' can't do if you know wha' I mean it's…. pretty.. average.
SONYA: it's jus' tha'.. the things with the diet.. there is no'.. they are no' things that she would eat… excessive amounts of anyway so that doesn't really apply..
SONYA: umm….. an' then we are always careful if she is climbing anyway an'…… it's jus' bein' a little bi' more careful if she falls an' hurts herself isn' i'? it's jus'..
INTERVIEWER: aha. So umm those things that umm.. errrr… you need to take care about.. with warfarin.. were you.. errrrmmm doing the same things with aspirin or it maybe..

SONYA: no' re'..
INTERVIEWER: a bit more..
SONYA: no' really.. with.. with the aspirin she never.. she n't really have any side effects with the aspirin.
SONYA: errrmm…. So i' didn' really.. she's never really been in an instant where she's fallen an'.. banged her head.. quite hard or.. she's not really.. had i'.. she's hadn' any trauma till her op or anythin' like tha' so we've no' really…. umm… bu' she never.. bruised any.. more than.. any of the other children running round nursery so.. with the aspirin.
SONYA: an' she hasn't too much with the warfarin actually.. either.
INTERVIEWER: OK.. so far (laugh).
SONYA: so far (laugh) touch wood (bang on the desk).
INTERVIEWER: (laugh) yeah because (laugh) yeah because she's like.. you know.. regard'.. like as newly started..
SONYA: yeah.
INTERVIEWER: only.. only it's a few months of..
SONYA: yeah.
INTERVIEWER: errrm warfarin.
SONYA: so we.. we're definitely more **careful**.. we're more **aware**.. with the warfarin.. than we were… with the aspirin bu' that's purely because we've.. been **told**.. by the professionals that the warfarin 's… a bi' more.. no' risky.. you just have to be a bi' more careful.
INTERVIEWER: OK. So are you aware of what umm… like maybe… adverse effects of warfarin?
SONYA: so…
INTERVIEWER: if the INR like goes high..
SONYA: (at the same time) internal bleeding..
INTERVIEWER: (at the same time) or goes low.
SONYA: could be..
SONYA: umm so if she bangs herself.. that what we've always been told to look out for if she 's.. takes a big blow to her head.. to take her to a hospital.. either way.. so i' could be internal bleeding.. umm… bruising.. obviously… bruising easier… umm…..
INTERVIEWER: yeah OK.
SONYA: so it's bruising an' bleeding.
INTERVIEWER: so how about when.. err.. if the INR goes very low?
SONYA: lower blood clots I imagine possibly…. Ummm… I don' know any other effects.
INTERVIEWER: OK.
SONYA: which have though.
INTERVIEWER: umm.. err.. soo yeah… umm.. so let's go back to thee.. your err.. you know.. those umm.. INR and.. measurements and you need to go to come to the hospital because you don't have the machine how do you.. see that umm.. frequency of… INR measurements?
SONYA: it's.. there is no… it's jus' random (laugh) i' completely.. we haven' managed to.. stabilise… I don' know anyway because you tell us when to come back don' you we haven' managed to satbilise.. umm.. say like.. I know some people who come every three weeks..
INTERVIEWER: aha.

SONYA: or have those done every three weeks bu' they've been on warfarin quite a while.. umm.. whereas with [child] she's jus' shshsh all over the place.
INTERVIEWER: OK.
SONYA: it's no' it's no' too bad.. and.. it doesn' it dosen' bother us havin' to come to get i' done because.. we know she needs i' doin'.. umm.. an' I'd rather have it done than.. have to deal with..
INTERVIEWER: so..
SONYA: any formal side effects with it so.. (laugh)
INTERVIEWER: yeah.
SONYA: it's no'…
INTERVIEWER: yeah.
SONYA: it's no' ideal bu' it's no'…… it's no' a pain.
INTERVIEWER: OK. So err do you need like to take some time off school umm?
SONYA: no she's.. well thee.. the liaison nurses have been really good about i' an' they've said.. umm.. because she finishes school at quarter pas' three.. bu' obviously we don' ge' back to the car till abou' tweny pas' tweny five past depending on how slow she's been umm.. an' they've if we jus' come straight from school then whenever we ge' here.. we ge' here an' that's when they do i' so they've been good about i'.. so she's no' had to miss any school or….
INTERVIEWER: OK.
SONYA: so far.
INTERVIEWER: so about.. umm.. err.. I need to ask about.. the dose.. of warfarin.. errmm.. who do you think that err.. should take this responsibility of deciding the dose?
SONYA: you (laugh).
INTERVIEWER: (laugh).
SONYA: I thought that's who did i'.
INTERVIEWER: apart from me..
SONYA: a pharmacist.. I would imagine.. maybe..
INTERVIEWER: is it like err.. do you prefer it like a doctor maybe?
SONYA: somebody who knows what they're doin' I don' mind who it is.. because they know..
INTERVIEWER: OK.
SONYA: what they're doin'.
INTERVIEWER: are you happy with what we are doing?
SONYA: yes. Yeah yeah yeah.
INTERVIEWER: and and how about this like dose changes?
SONYA: it's.. it's fine it's fine. We've no' had anything.. her dose.. her doses.. tend to be over a similar pattern so it's no'.. we've no' had anything.. drastic.
INTERVIEWER: umhm.
SONYA: any drastic changes and… they're easy to remember so it's no'…..
SONYA: we're fine with i'.
INTERVIEWER: OK. So and er er as far as I know she is on thee err solution or the liquid warfarin..
SONYA: (at the same time) liquid yeah.
INTERVIEWER: do you find it easy to use?
INTERVIEWER: yes. She loves i'.
INTERVIEWER: Oh! Great.
SONYA: (laugh).

INTERVIEWER: (laugh).
SONYA: yeah. which is..very easy.
INTERVIEWER: aha… and umm.. errmm.. how about.. umm you know adjusting the dose with the liquid form?
SONYA: it's fine.. it's easy it's probably easier to adjust with liquid form than it is… with a tablet I'd imagine.. I do' I don' know because we haven' used the tablet bu'.. with the liquid it's just…
INTERVIEWER: so you have never used the tablet even when..
SONYA: no' with the warfarin no.
INTERVIEWER: even when you were.. inpatient like.. when [child] was.. in the hospital..
SONYA: no' for the warfarin no.
INTERVIEWER: for the first time?
SONYA: no no. we used with her aspirin.. umm…. bu'.. tha' was really really easy because she was on.. 37.5 milligrams which was half a table'.. umm.. so we jus' dissolve the whole table' an' give a half so tha' was… very easy.
SONYA: bu'.. I don' know whether with warfarin tha' migh' be a little bi' more difficult because the doses vary so much don't they?
INTERVIEWER: OK. So.. yeah.. so you were fine with the um those.. umm dose changes?
SONYA: yes.
INTERVIEWER: ummm.. so er.. yeah.. so.. in your experience so far what errrr…. you.. what have you found that ummm might affect this.. warfarin dose?
SONYA:…… I actually have no idea… I really don't know.
INTERVIEWER: ha'.. haven't you been in some situations where you realise that those particular things affect the INR..
SONYA: no..
INTERVIEWER: make it go up or..
SONYA: (laugh) no.
INTERVIEWER: (laugh).
SONYA: I actually haven't.. (laugh).. I would like for somebody to tell me wha' affects tha'… 'cause I.. I..
INTERVIEWER: (at the same time) maybe like some..
SONYA: haven't got a clue.
INTERVIEWER: let's say.. maybe her diet?
SONYA: … Oh… pass.. she is.. pretty much the same things.. all the time.. she doesn't really.. have any….. I don't know.
INTERVIEWER: like umm.. it's like.. you know ummm.. her normal.. her.. er regular diet?
SONYA: yeah.
INTERVIEWER: and you are adjusting.. the err… warfarin or the INR with it?
INTERVIEWER: there hasn't been like..
SONYA: (at the same time) err..
INTERVIEWER: massive changes..
SONYA: we haven' changed her diet at all because thee…. the list of foods that we were given that we should.. so we were give a list of foods that we should.. just.. stay clear of.. ones that we should be careful with..

SONYA: umm.. ones tha' she can have a bi' of.. bu' no' an excessive amount of an' she doesn'.. the only one on there tha' she likes.. anyway.. is broccoli.. but she'll only have.. like one or two stocks.. maybe twice a week so.. it's no'… she doesn' have an excessive amount of any of this.. tha' kind of food anyway.
INTERVIEWER: what other types of food that ummm
SONYA: (at the same time) err..
INTERVIEWER: (at the same time) you were made aware of.. that might affect.. the INR?
SONYA: I can' remember…. I know this had anythin' green pretty much (laugh).
INTERVIEWER: (laugh).
SONYA: which is she doesn' ea' anyway.
INTERVIEWER: so.. so.. what I can understand..
SONYA: cranberry juice.. I know cranberry juice is err.. an' cranberries bu' she doesn't like.. she doesn' touch tha' anyway so.. that's no' an issue.
INTERVIEWER: OK.
SONYA: yeah.
INTERVIEWER: so.. so you took that ummm.. errrr.. list of.. let's say diet..
SONYA: yeah.
INTERVIEWER: and err..
SONYA: I'm tryin' to remember what's on i' now.
INTERVIEWER: yeah.. so..
S making signs indicating that she can't remember
INTERVIEWER: but.. (laugh) you made it like.. you know tailored it to her.. (laugh).. usual..
SONYA: well I looked a' i' an' I thought it's no'… i' ge' a falls in place with her die' anyway so we haven' had to…
INTERVIEWER: OK.
SONYA: change anythin' really.
INTERVIEWER: so..
SONYA: yeah.
INTERVIEWER: er OK, that's with diet..
SONYA: unless there's something I don' know about that's affecting her INR..
INTERVIEWER: well it's usually.. e' everything sh'.. should be there on that list..
SONYA: yeah.
INTERVIEWER: but you need to.. umm.. be aware of..
SONYA: yeah.
INTERVIEWER: ummm.. so how about other.. er medicines?
SONYA: …… Oh I don' know.
INTERVIEWER: antibiotics maybe?
SONYA: yeah we haven' had any of those yet since she's been on… INR so we haven' had that experience ye'.
INTERVIEWER: err.. any ummm..
SONYA: she's now on.. diuretics.. she's on spiro (spironoactone) an' furoso (furosemide).. and.. movicol.. an' ranitidine. bu' she's been on them… all a long anyway.
INTERVIEWER: yeah. So up to now she is on those err..
SONYA: yeah.
INTERVIEWER: stuff.

SONYA: so I don' know if they affect her INR or no'….. I don' know (laugh).
INTERVIEWER: (laugh).
SONYA: I jus' give her wha' I'm told. (laugh)
INTERVIEWER: OK (laugh). So and.. umm any other.. errmm.. may be illnesses.. that ..she might have been… through?
SONYA: she.. she's no' been poorly she's had.. a cough.. an' tha's about i'.. since she's had her op. touch wood.
INTERVIEWER: (laugh).
SONYA: which is brilliant for her.. it's very good she's no' had any..
INTERVIEWER: yeah.
SONYA: I assume maybe sickness an' diarrhea tha' possibly would tha' affect i'?
SONYA: tha' seem to affect everything doesn' i' I don'.. bu' she's no' had any of tha'.
INTERVIEWER: any types of maybe fever or something.
SONYA: yeah.
INTERVIEWER: she hasn't got any.. of that?
SONYA: no.
INTERVIEWER: errrr.. I can't remember is that.. was that o'.. [child] that had ummm chicken pox?
SONYA: Oh she did bu' tha' was before…. tha' was before her op.
INTERVIEWER: after.
SONYA: was i'?
INTERVIEWER: because yeah I I can remember that..
SONYA: Oh i' was after her op
INTERVIEWER: yeah.
SONYA: because we couldn' to bring.. we were no' allowed to bring her in.. for her INR..
INTERVIEWER: yeah.
SONYA: because she had chicken pox yeah.
INTERVIEWER: yeah.
SONYA: sorry. (laugh)
INTERVIEWER: (laugh) it's alright.
SONYA: mum brain (laugh).
INTERVIEWER: yeah so.. umm during that period have you found that er.. there.. umm.. was something.. umm… her dose needed to be adjusted.. or.. the INR went up or something?
SONYA: we didn' have a test did we when she had the chicken pox so I don' know.
INTERVIEWER: um.
SONYA: we didn'.. we had i' tested like the week before.. an' then the week after an' I.. honestly I should 've brought my book 'cause I can' remember wha' the INR as well.
INTERVIEWER: yeah.
SONYA: umm.
INTERVIEWER: I can remember that the.. the doctor has recommended to decrease the dose.
SONYA: yeah. (laugh)
INTERVIEWER: yeah because I was doing the computer dose and then.. umm.. the doctor decided to decrease that.
SONYA: decrease i' while she has chicken pox?
INTERVIEWER: yeah.

SONYA: yeah.
INTERVIEWER: and asked if there were any.. like sign of.. bleeding or bruising..
SONYA: Oh yeah they did say to me if there is any.. bleedin' under the skin..
INTERVIEWER: yeah.
SONYA: or on the spots then to.. ring.. straight away. bu' she didn' ge' any of tha' she had.. she had a very mild case to be fair she only.. had 8 or 9 spots.. an'..
INTERVIEWER: so yeah and and umm.. what.. kind of medicines that she err have got.. has got form.. while she were..
SONYA: with the chicken pox?
INTERVIEWER: yeah.
SONYA: I jus' gave a calpol.. I didn' give.. jus' gave a calpol.
INTERVIEWER: OK.
SONYA: I know some people who give like Piriton an' stuff weren't they for itching..
INTERVIEWER: sorry?
SONYA: some people give Piriton.. an' stuff for itching.. bu' she was… I jus' gave a calpol. She was fine.
INTERVIEWER: so it was mild?
SONYA: yeah. Ya ya ya very mild.
INTERVIEWER: umhm… umm.. yeah.. so.. umm…. those that are the main things umm.. err.. that I need to ask umm you know.. err your experience with warfarin.
SONYA: yeah.
INTERVIEWER: err so do you have any.. errr other things that you like to add?
SONYA: umm..
INTERVIEWER: err..
SONYA: the only thing I will add is.. tha'.. I exp'.. she hasn'.. with the bruising an' stuff 'cause we were warned abou'.. bruising weren't we… an' like you said she's only put on i' a short time bu' we haven' noticed any.. drastic changes we have the ank' bruise where.. I wouldn' say she's bruised easier.. bu' the knock she had caused like er.. nastier looking bruise than i' normally would.. umm.. bu' we've no' had any…. major bruisin' or… anythin' bigger than.. a ten p. (laugh)
INTERVIEWER: aha OK.
SONYA: bu' she's quite impressive I thought i' was.. glad abou' tha'.
INTERVIEWER: yeah so ummm errm any other maybe concerns.. regarding this whole.. warfarin treatment.. err.. whether it's regarding.. the INR monitoring.. the doses..
SONYA: umm..
INTERVIEWER: maybe the overall… thre'.. therapy?
SONYA: we are as happy with i'.. as you can be for bein' on warfarin (laugh).
INTERVIEWER: (laugh).
SONYA: no were umm… we don' have any complaints I mean… obviously the comin' to.. havin' to drive to hospital to have her INR done.
SONYA: is a li'le bi' incovien' **bu'**.. it needs doing so…it's no' the end of the world and.. I'm imagining at some poin' along the line.. they migh' receive some machines for us to me be do i' a' home (laugh).
INTERVIEWER: (laugh) yeah.
SONYA: so we.. it still very new for us isn' i' so we just… just go along with i'.
INTERVIEWER: aha. So do you find it easy to go?

SONYA: yeah it's no' difficult…. the the… the liaison nurses are very.. umm flexible with i' as well we're like.. we're meant to be coming.. next Tuesday.. bu' [child] does swimming lessons on Tuesday so they've said well.. come Monday or Wednesday they're no'… they.. very much would do i' around our schedule rather than… tellin' us she have to be here on this day at this time.. which would make i' more difficult.. so no it's pretty easy.
SONYA: jus' keep to.
INTERVIEWER: aha. And umm how about.. err.. er just er.. I got that in my mind list of umm.. thee medicines.. have you been given any list of.. maybe medicines that er to avoid or to take care about?
SONYA: no.
INTERVIEWER: so any medicines that interact.. may interact with warfarin go.. make the INR go up or..
SONYA: no (laugh).
INTERVIEWER: (laugh)
SONYA: Should I have been?.. No no one's given me tha'.
INTERVIEWER: aha. So an'..
SONYA: maybe I should ask for one of those.
INTERVIEWER: umm. and no one has told you about anything about you know medicines that may… affect the INR go up or down?
SONYA: no.
INTERVIEWER: OK. Yeah so any other comments? overall?
SONYA: no' tha' I can think of… I'm pretty happy.. as happy as we can be (laugh).. no it's good.
INTERVIEWER: alright great.
SONYA: it's been easier than we though' i' would be.. which is nice.
INTERVIEWER: so at the first time you thought that it would be..
SONYA: Oh yeah we thought i' would bee.. pretty…. well.. we thought i' would be more… I don' know how to describe i'.. we thought i' would worry us more than i' does bu' we're.. we go on.. abou' things.. as we did.. before pretty much we jus' know in the back of our heads.. to be a li'le bi' more careful with her.
SONYA: bu' she still does evry thing.. an' more.. than she did before her op so..

**4- Interview number 11: Participant 1005's mother**

INTERVIEWER: um good morning and thanks you so much for coming and.. for agreeing to take part in my research…ermm the purpose of.. our meeting is to.. talk about.. err [child's] warfarin therapy and err.. erm how best you manage that.
KAMYA: OK.
INTERVIEWER: ermm.. it is important.. that I get to know.. how it is for you.. err managing ermm.. [child's] warfarin therapy.. ermm.. I imagine that this has been very new for you..
KAMYA: u'um.
INTERVIEWER: and.. errmm it.. looks like that it.. you have been on a bit of journey.. erm.. to learn how.. to manage warfarin for [child]..
KAMYA: OK.
INTERVIEWER: errmm so I.. would like to start off by… erm asking you to think back to the first time when the doctor.. or.. may be the nurse.. first explained what warfarin therapy is and why [child] needs to take it.

KAMYA: ya. Errmm.. err it's been explained that err it is very important medicines for [child].. and she has to take it as er.. like er.. modern.. er.. types of medicines that er.. helpful for the cardiac patients especially.. like [child].. so.. it is very useful for her to take and st'.. er means to tinner (thinner) the bloods.. and.. for the… smooth circulation of the blood so… er in that sense er we have accepted er.. that er.. yeah.. errm if it is so good for [child's] health so we'll accept it yeah.
INTERVIEWER: OK. Errmm so.. errmm as you said it.. it ermm helps to thin the blood any more information.. ermm.. you know about warfarin.. why erm.. why it is especially needed for..
KAMYA: (at the same time) yeah.
INTERVIEWER: (at the same time) these circu'.. for.. [child's] surgery?
KAMYA: yeah. Err it's been ex'.. explained that er.. warfarin is a tablet.. ummhhm.. that err.. control the circulation so sometimes it's high it's err.. errmm.. when the.. bloods become.. too tin (thin) then we have to.. lessen the dose..
KAMYA: or.. if it is more thick then.. err.. the dose has been increase. So.. er according to the INR means the blood.. err.. go'.. errmm.. the ratios.. err the warfarin dose has been fluctuatin' an' it's been flexible so.. it is not like a regular dose like aspirin we have to take once a day.. two a day.. it's not like that.
KAMYA: it has to be.. errmm regulated and it has been control an' it is flexible changing.. the dose.. err.. ar'.. according to the bloods yeah.
INTERVIEWER: erm so er how do you feel about erm being involved in this process of warfarin monitoring?
KAMYA: yeah it's er feel quite satisfied that err… we are.. in the safest zone like er.. we are.. err.. it's not going to happens.. means err.. errmm any difficulties or any kinds of problems that may occur in futures because everything is in control so… it's quite satisfacting an' we.. feel that it is.. good for her an'.. for us also.. that err… testing the INR every time an'.. er.. changing the dose all the time it means that it shows that e'.. she is in a stable conditions.
INTERVIEWER: OK erm so erm let's go.. back to the.. you know.. for the.. first time.. when the.. erm the doctor.. or maybe the nurse errmm.. gave you the information about warfarin..
KAMYA: (at the same time) umm.
INTERVIEWER: (at the same time) and how to monitor it.. erm.. can you please tell me more about that?
KAMYA: OK errmm.. that explain as err.. well ermm by providing hers the.. the.. manuals..
INTERVIEWER: (at the same time) sorry?
KAMYA: the manuals.
INTERVIEWER: aha.
KAMYA: they given us a manual.. err I go trough (through) the manuals and read what's the effect what's the sides effect what's the benefits.. everything I've gone trough (through).. an'.. also the doctors.. and the nurse have explains that.. how.. err.. warfarin.. err.. useful for the [child]..
KAMYA: an' ermm.. they 's explain us.. err.. errmmm… yamm like… I'd said that err.. it helps the blood circulations that occurs and the.. the clots has been.. err manage an' everything else they had been explained.
KAMYA: an'.. more of the benefits I've got from the manuals reading the manuals so.. everything is clear listed it in the manuals that.. what..

INTERVIEWER: so were errmm those manuals were they like erm easy to read and to go through?
KAMYA: (at the same time) yeah yeah yeah it was quite easy and quite beneficial so I can understand it it's very easily.. yeah.
KAMYA: as a parent I can easily understands like.. language of the doctors.. sometimes.. err it's confuse but..manuals.. make it little bit clear.. more about clear us. yeah.
INTERVIEWER: so.. errmm about errmm.. you know.. managing this.. er warfarin.. errm therapy with her.. let's say.. daily life.. erm.. do you find it easy to manage that?
KAMYA: …. Yeah it's not too much complicated because once in a day.. she has to take 'er medicines an' now it's become like a **routine** that.. before going to sleep… she takes 'er warfarin.
KAMYA: so… it has become like a routine that err.. she has to take the dose an' err.. it has become like a **habit** so… more or less.. it's not a much problem.. it's very easy.. an'.. it is very comfortable as well.
KAMYA: so.. it's not like err twice a day tris (three times) a day.. she has to take 'er medicine it's only once a day an' that's also.. bedtime. easy to manage (laugh) yeah.
INTERVIEWER: OK. Errmm so how about like errmmm other things.. errr.. like erm her diet.. errm if she is.. like.. taking other medicines.. erm how do you fit that with warfarin?
KAMYA: … err it has been explained that some kinds of medicines are restricted with the warfarin.
KAMYA: like antibiotics ibuprofen so… err.. we are aware of that.. an' even that [child] has been aware.. er I had made her aware that.. such types of 'e medicines you have to… errm.. be careful… while taking with the warfarin.
KAMYA: otherwise.. errmm.. err.. with oder (other) medicines it's OK.. doctor has suggested as per the suggestions has been a prescriptions… advice of the doctor.. we are giving the medicines regularly.
INTERVIEWER: so at the moment which medicines.. err.. she is..
KAMYA: (at the same time) she is taking.. er sildenafil tris a day three time a day.. err furosemide once a day an' lisinopril once a day. an'.. warfarin.
INTERVIEWER: OK. And err for those er.. medicines that.. erm.. she.. you were errmm.. err.. like were made aware of.. like the antibiotics and.. ibuprofen and stuff, has she ever needed to use the?
KAMYA: no no, not yet.. not yet. No.. no such kinds of condition has been occurred like err.. for.. err.. severe pain so that I can give ibuprofens or.. err..
INTERVIEWER: (at the same time) so she's been..
KAMYA: (at the same time) antibiotics..
INTERVIEWER: (at the same time) well since..
KAMYA: (at the same time) yeah yeah she's she's heal'.. healdy (healthy).. taking diet properly..
INTERVIEWER: (at the same time) alright (laugh).
KAMYA: (at the same time) eating all the times mean..
INTERVIEWER: (at the same time) alright.
KAMYA: (at the same time) so.. no problem at all touch wood yeah.
INTERVIEWER: (laugh).
KAMYA: (laugh).

INTERVIEWER: alright. So.. and and how about her diet, how you manage that with warfarin?
KAMYA: err **normally**.. I can has to means err.. whatever the normal.. diet she has to take.. I won't… used to take.. much care that… you won'.. eat that.. you won'.. eat.. whatever she wants, but I.. usually prefer the healdy (healthy) foods.. to hers.. no junk.. no.. no more junk foods.. sometimes.. err the childrens wants like err… pizza an' err burger an' also.. once in a week or..
INTERVIEWER: (at the same time) yeah.
KAMYA: (at the same time) I used to take..
INTERVIEWER: (at the same time) yeah of course yeah.
KAMYA: (at the same time) but a r'.. regular diet err.. I'm concenting (she may mean concentrating) on the regular diet and she also take perfectly the reg'.. the diet..
INTERVIEWER: (at the same time) OK.
KAMYA: (at the same time) an' all this food.
INTERVIEWER: so.. erm have you got a list of.. diet that may.. may interact with warfarin?
KAMYA:… ermm.. diet ermm.. er no but since yet I have not interact with the diet means.. I have not concentrated on her diet.. with the warfarins.. because.. err.. I say that erm.. err.. in form that vitamin K is useful.. means err.. has to be maintained like.. green vegetables or… like errmm… alls type of spinach or green leaves vegeta'.. leafy vegetables I used to prefer.. the soups an' all.. to her.. that so that she can maintains err.. with the.. warfarins yeah.
INTERVIEWER: so.. er were you made aware of any type of food to.. like.. take care of?... not to take in excessive amount?
KAMYA:… ah ya.. ya so…. Err excess amount means err… o' her.. like her.. errmm according to her age.. she won't take some.. more like er.. everything in the.. err right proportions.. right means.. not more not less..
INTERVIEWER: OK.
KAMYA: if she likes something er.. er with a green vegetables she won'ts go on eating the green vegetables all the time.
INTERVIEWER: (at the same time) of course (laugh).
KAMYA: (at the same time) (laugh).
INTERVIEWER: (at the same time) does she does she like the green.. vegetables?
KAMYA: (at the same time) yeah yeah yeah she likes the salads an' all.. too much.. but err.. but she takes like.. not all the day the green vegetables.. once in a day..
INTERVIEWER: OK.
KAMYA: like.. so.. all kinds of foods like pulses.. errm meat.. fish.. everything.. once in a day she used to take so.. she is like very.. err fully like.. (laugh)
INTERVIEWER: (laugh)
KAMYA: so.. she needs all kinds of foods means not.. err.. stucks on a one.. that rice.. or chapatis.. no not that.
KAMYA: er.. she.. every.. er.. erm.. all the day.. she needs some.. different kinds of foods (laugh)
INTERVIEWER: (laugh) aha.
KAMYA: so I have to manage that (laugh).
INTERVIEWER: alright. Ermm so erm yeah.. ermm so.. like erm you are aware of what type of food that.. that may interact with warfarin and cause like.. **disturbance** in

her INR…aren't you? Any type of food so… anyone told you about err.. specific types of food that may interact with warfarin?
KAMYA: .. ermm.. no.. still yet not.. err.. I have.. I have no idea about err..
INTERVIEWER: (at the same time) in your.. in the.. the list of er.. or in the manual.. that you were given er.. was it.. ever mentioned that erm.. certain types of food that.. interact with warfarin? so.. you have to take care about?
KAMYA: ermmmm I don't have much idea about that, sorry.
KAMYA: errmm but errr… errmm.. I had been informed that err.. she has to take some green vegetables..
KAMYA: more in amount.. so it's good for her.
INTERVIEWER: more or less?
KAMYA: more or le'.. means errrr… what you say like err…. er is the INR..
INTERVIEWER: (at the same time) balanced.. amount like?
KAMYA: sorry?
INTERVIEWER: balanced amount?
KAMYA: yeah, the balance amount means not more not less.. as I said as she is fond of er.. er salads an' all, but she takes once in a day.
KAMYA: not all the time.
INTERVIEWER: OK.
KAMYA: yeah?
INTERVIEWER: yeah.
KAMYA: so… it has been in a.. proportions like.. it is the ratios all the time it's going so.
INTERVIEWER: OK.
KAMYA: yeah yeah.
INTERVIEWER: errmm so yeah. And now back to the.. err.. this monitoring process of.. the dose.. and the INR who.. er.. do you think should take the responsibility.. of.. monitoring INR?
KAMYA: … mmm the brought her hospitals, myself.. parents as a parents.. errmm… er everybody is responsible for that (laugh).
INTERVIEWER: (laugh).
KAMYA: (at the same time) because..
INTERVIEWER: (at the same time) alright..
KAMYA: (at the same time) yeah.
INTERVIEWER: (at the same time) can you please..
KAMYA: ah yeah.. so.. it's all according to the advice of the hospitals, the doctors, they says.. that err.. this much dose has to be given.. and.. this day she has to be check the INR.
INTERVIEWER: umhm.
KAMYA: the reports of the INR has to be submitted on this day, so it is err.. once they say.. they recommend err that.. so an' so dose an' so an' so days, err.. he has to be.. she has to be check.. then it is my responsibility that I have to.. carry out all this, yeah?
INTERVIEWER: alright, alright. So and about.. you know.. deciding.. this.. errm dose of.. when you.. when the hospital tells you that erm you need to give this dose and to.. monitor.. erm.. erm.. do you find.. ermm like ermm do you feel that this is err the right person or you need to do the dosing yourself or.. who who do you think the best judge..
KAMYA: (at the same time) no.
INTERVIEWER: (at the same time) to get this dose..

KAMYA: (at the same time) yeah yeah.
INTERVIEWER: (at the same time) and monitoring right?
KAMYA: of course I can decide it myself because.. er I.. just follow the instructions.. all the doctors and the hospital says.. err and the experts of warfarin says. so.. I can decides of myself that how many dose I.. used to gi'.. I.. feel that.. I.. no doctor has said 4 but I used to give 2, it's not that. Err once it is said that er 4.. 4 m g (milligram) per day.. then I have to follow.. strictly.. the 4 m g per day (laugh).
INTERVIEWER: (laugh) alright.
KAMYA: yeah (laugh).
INTERVIEWER: so yeah you you prefer to.. like..
KAMYA: (at the same time) yeah yeah..
INTERVIEWER: (at the same time) follow what the doctor's..
KAMYA: (at the same time) yeah yeah..
INTERVIEWER: (at the same time) advice?
KAMYA: advice yeah of course.. of course.
INTERVIEWER: OK.
KAMYA: mm.
INTERVIEWER: erm so and errm then.. errmm.. how about your responsibility in the house.. err..
KAMYA: yeah everybody is responsible for that (laugh).
INTERVIEWER: (laugh).
KAMYA: 4 m g means 4 m g.. everyday (laugh).
INTERVIEWER: (lagh).
KAMYA: 3 mg means 3 m g everyday, everybody is responsible to look after that she has taken 4 m g.. per day or not yeah?
INTERVIEWER: alright. And ermm how about you know the.. this number of INR measurements how do you feel about that?
KAMYA:… yeah.. I feel that errmm.. as per the dose.. according to the dose.
KAMYA: errmm the INR changes so.. I.. jus' err notice.. the changes.. that someti'.. when the dose is less.. INR is also comes less means err it's like.. her normal range is 2 to 3.
KAMYA: so… if I foun' it is 2.. or two point zero (2.0) or 2.1 2.3 I think that she needs some more.. like err.. err more doses in. But err.. as per the doctor suggestions they says that.. she has to be given 4 m g 3 m g I strictly follow that.
KAMYA: then… whatever maybe the results.. it's upon.. the doctors and the.. experts yeah?
INTERVIEWER: OK. Errm I mean.. you know the frequency of INR measurements how frequent you need to come to **hospital** and.. test the INR how do you find that?
KAMYA: yeah errmm… err twi' er once.. in er.. 15 days that e'.. two.. er once in a two err two weeks..
KAMYA: err it's OK. But now.. as the charity has provided us the machines 'at at home so.. we used to do it at home an'.. they had also recommended that.. every two week er.. 'at she has to be monitored.
KAMYA: (at the same time) an' I was..
INTERVIEWER: (at the same time) so now you have got the machine at home?
KAMYA: (at the same time) yeah yeah machine at home yeah..
KAMYA: yeah. An' before that I was coming.. every two weeks in the hospital for err.. for the test.

INTERVIEWER: so.. how.. was it.. how do you.. how did find that you know.. coming to the hospital every two weeks… how did you find that?
KAMYA: …. Errmm.. yeah it's OK I can manage it err.. to come to the hospitals an' do the test so… err it's not much a problem like.. yeah.
INTERVIEWER: so.. you .. do.. like erm did you need to take like some.. time.. off.. work or take erm..
KAMYA: (at the same time) yeah of..
INTERVIEWER: (at the same time) [child] off school?
KAMYA: yeah yeah errmm… err.. school already knows about the.. her health conditions.
KAMYA: so I already.. been explained that err.. she is on warfarin an'.. she has to be.. err.. tested so.. as per.. the hospital. So.. any time I need to go means er.. they had been.. suggested that err.. err.. I 've been calling after two.. two weeks. So they.. most probably **know**.. that today is 'er test day.. or Friday.. I have to go for the blood test so..
KAMYA: they directly give the permissions regarding that. An' also.. err.. err.. I had suggested to the hospital that.. Thursday Friday is my off day.. so I manage to come so it's easily.. err I can manage it yeah.
INTERVIEWER: aha. OK. And errmm.. errmm this is errmm.. erm you.. like erm.. so it was OK for you..
KAMYA: (at the same time) yeah yeah.
INTERVIEWER: (at the same time) managing that coming to the hospital..
KAMYA: (at the same time) yeah it's OK.
INTERVIEWER: (at the same time) and.. doing the test.
INTERVIEWER: and errmm how about the.. errmm the dose changes so n' you know every time like you get.. a different dose how did you feel about that?
KAMYA: … yeah I feel that errrmm.. whatever has been suggested it is good for her.
KAMYA: so… (laugh).. I don't err.. include myself means err.. my suggestion or my advice because I'm n'.. not.. much.. experts an'.. 'm not.. aware.. about.. all these things so… whatever.. has been told to me I strictly follow.. it yeah.
INTERVIEWER: so.. and erm I mean errmm… errr.. errmm you know.. so the d'.. the.. so did you find it OK to like.. you know.. make those.. d'.. d' those.. err dose.. changes?
KAMYA: yeah yeah.
INTERVIEWER: like.. was it easy for you regarding..er as far I..
KAMYA: (at the same time) yeah yeah.
INTERVIEWER: (at the same time) as.. I know she is taking the tablet so how you manage that?.. with tablet. Was it easy or.. did you find it difficult like..
KAMYA: (at the same time) no no..
INTERVIEWER: (at the same time) with the tablet?
KAMYA: (at the same time) it's easy it's easy because er.. as per the dose er.. I get my.. medicines from my surgery..
KAMYA: so… I easily manage.. to get.. I can say that er.. it is er.. recommended er.. such a dose.. in er.. once a days that's 4 m g (milligram). It's frequently changing.. so they also cooperate an' I.. I get the medicine easily.. er warfarin er.. from my.. pharmacis'..
KAMYA: so nearby..
KAMYA: so.. it's easy to.. manage all those things it's not much difficult then… not med' err.. problem get it at all.

INTERVIEWER: aha. Errmm… so.. errrm… errm.. do you have any other errmm… concerns about… err.. warfarin treatment with.. for [child]? Anything that erm.. you may be concerned of?
KAMYA: errmm.. the concern means errr.. it may happen that er.. suddenly I have to go.. out means abroad.. for the holidays.. an'.. I have to manage.. with this dose..
KAMYA: everything else so.. I feel **that time**.. but.. it won' **happens** all the time like..
KAMYA: err once in a year.
INTERVIEWER: OK.
KAMYA: or.. once in a two year.. it may happen.
INTERVIEWER: umhm.
KAMYA: but not it's.. frequent so… I don't think so that it's a problem an'.. if it's a problem then.. it can be easily manange. Because er.. the thing has to do is to follow the dose.
KAMYA: as per.. the INR yeah?
KAMYA: so… err.. if I am abroad.. I can err.. send err.. INR test trough (through) email.. I have the telephone contacts.
KAMYA: whatever so.. err.. I can manage it yeah (laugh).
INTERVIEWER: OK.
KAMYA: yeah.
INTERVIEWER: errmm.. so.. any other concerns regarding let's say the.. maybe the side effects of warfarin?
KAMYA: err yeah. Err it is said that err.. the overdose may cause.. a bleeding and the less dose may cause the clot.
INTERVIEWER: OK.
KAMYA: yeah? so… ummm.. the mm dose.. means the warfarin.. that is given to her.. errr.. the dose that is given to her.. that was… according.. err.. er to her INR an'.. it has to be maintain.. an'.. err the ratio has to be maintained for the lifetime yeah?
KAMYA: so.. what.. the standard has been err..
INTERVIEWER: yeah. So other things like errr.. maybe.. errmm maybe concerning to you like.. you know she is a child, she might be… err predisposed to bruises or things like that.. err has she ever got something like that or maybe nose bleeds or things like that?
KAMYA: um um um.
INTERVIEWER: because she is on warfarin?
KAMYA: um um um.
INTERVIEWER: so ermm.. ermm.. has she got anything like that?
KAMYA: n'.. not yet because err she's just now.. 9 years ol' an'.. all this problems err… I think after two or three years err will come an' will face all.. all these difficulties after two or three years.
KAMYA: so… n' er now he is a chil'.. she is growing.. young.. so… now it's going everything OK.. but.. when these problems occur.. I think I get an experience after that (laugh).
INTERVIEWER: (laugh) OK..
KAMYA: (at the same time) what to do (laugh).
INTERVIEWER: (at the same time) so touch wood there is nothing (laugh).
KAMYA: (at the same time) yeah yeah of course (laugh).

INTERVIEWER: so yeah errmm.. so anything else ermm that you would like.. er to add.. errmm for the.. you know.. the overall process of like.. warfarin.. errmm treatment.. for [child].. any concerns that you..
KAMYA: yeah.
INTERVIEWER: (at the same time) may have?
KAMYA: there was some doubts err regarding this dose that when she grow.. **young**.. errmm.. what will the problems err regardings her periods regardings her pregnancy an' all.
KAMYA: so…mmm.. the expert has er.. Madison has explained me.. that er when she grow.. at that time.. may occur.. excess bleeding.. errmm due to warfarin when she get pregnants..
KAMYA: err then.. it's.. warfarin is.. not good for the fetus. So at that time.. they will.. sugges'.. that what treatmen' or what kinds of err.. err dose or what er.. for the treatmen' or what.. procedure they have to follow.
KAMYA: yeah so.. (laugh).
INTERVIEWER: alright (laugh).
KAMYA: so it's err.. out of her.. all my.. attentions an' all (laugh).
INTERVIEWER: (laugh) OK. Erm anything elso you would like to add.. about the overall process of.. warfarin.. treatment?
KAMYA: yeah I'm quite happy with all this treatments an' all an'.. our family alls are.. too much happy regarding all this er.. facilities an' all this er.. procedures that is.. going with the er.. er [child] an' it is good for her health an'.. I think that I had become attention free.. for her health for the lifetime (laugh).
INTERVIEWER: (laugh) OK. So and erm.. you know ermm.. er..erm.. this er.. your erm.. you know contact with the doctors and with the nurses.. ermm.. how do you find that regarding this..
KAMYA: (at the same time) it's.. it's very friendly I say it's very.. like.. I can't err.. err believe that er.. they are… the different peoples of my.. range or my family circles. I feel that all are family an' all.. like er our relatives like our brothers sisters an' all (laugh) they are helping they are.. too much helpful an' I.. I feel very.. close to them an'..
KAMYA: I feel very friendly.. to explain my views to.. accept their views.. everything is very friendly.
INTERVIEWER: so.. erm have you come.. have you ever come.. er er like had got an incidence where you discussed something with them regarding warfarin?
KAMYA: um um.
INTERVIEWER: er with the doctor or with the nurse like you had some concern and discussed that with them?
KAMYA: yeah of course then.. err yeah.. err.. I.. used to discuss with the Madison an' err.. she used to.. err.. give me.. err the.. right.. err suggestions and the right advice and the right recommendations that.. this has to be going to happen this has to be going to, so it feels very relax for me that everything is in the safe hand OK.
INTERVIEWER: OK. So erm can you please tell me like.. what.. type of things that ermm you were talking about like any.. erm.. apart from the pregnancy and the pre' periods..
KAMYA: mm.
INTERVIEWER: er other things like.. errmm have you.. queried about?

KAMYA: errr yeah er I had just asked about that er… if we are.. out of.. the country.. like we are going for the holidays or.. in the out.. other country so.. err.. at that time how can I manage errr how can I contac' you.
KAMYA: an'.. all that question has been solved so.. everything has been err suggested to me that you can do this this this, you can do.. that, you can phone us, this is our phone number, this is our email ID.. err this is our contac' so.. everything become very easy for me (laugh).
INTERVIEWER: alright. Oh brilliant.
KAMYA: umm.
INTERVIEWER: errmm so errmm one last thing se' errmm.. last comment if you would like.. anything you would like to add?
KAMYA: … (laugh) all about is err.. I'm satisfied. (laugh)
INTERVIEWER: (laugh) great.
KAMYA: yeah. It's no worry about at all an'.. err I think err it's err... biggest relas relax of my life that err I had been err.. facing for.. that I was been worried that for the life time.. I have to take care of her, I have to look after her.. health, I was worried about that what is going to.. happen to her in the life.. in the future life but err after..
INTERVIEWER: sorry was that regarding warfarin or regarding her..
KAMYA: no no before before warfarin but after.. that I feel that.. it is everything been OK.
KAMYA: an'.. now… er she can live a normal life.
INTERVIEWER: (at the same time) alright.
KAMYA: (at the same time) like other..
INTERVIEWER: so regarding her.. like her medical condition overall?
KAMYA: yeah yeah.
INTERVIEWER: and how about warfarin?
KAMYA: yeah the medical conditions.. before surgeries an' before warfarin.. that I said that I was.. too much worried about her future.
KAMYA: but err.. now I think it's.. she is in the safest han' an'… she can live, she can manage, she can understand.. what is going on, what the procedure is going on in her life.
KAMYA: so… she can.. err I think that in the future life she will understands that what has happened to her.. and what's going to happen with her.
KAMYA: so.. err…. so as a parent… we are very much satisfied.. an' as a patient [child].. er she is also very much satisfied an' she is also.. think that she is safe (laugh)..
INTERVIEWER: (at the same time) alright.
KAMYA: (at the same time) for the life in the future.
INTERVIEWER: so errmm.. err.. as [child] like you know.. she is 9 years old.. errmm is she aware of warfarin err.. or maybe you.. maybe you are trying to get her..
KAMYA: (at the same time) I'm trying..
INTERVIEWER: (at the same time) involved..
KAMYA: (at the same time) I'm trying to invol' an'… not like err.. everything I explains once in a day.
KAMYA: I used to… take one one sentence.. warfarin is a tablet that.. tinner (thinner) the bloods.. that circulates in the body an' make your body perfect.
INTERVIEWER: alright.
KAMYA: that's one sentence for the once a day.
INTERVIEWER: ahh!

KAMYA: (laugh) then the next day.. that err.. if you take a less dose, it thicks.. it become a clot.. you'll become lazy.. you won' be able to… do your normal activities. That's the second thing. So everyday I used to explain while giving her the dose that this is the, so… in this way she has came to know.. everything about..
KAMYA: what err is warfarin an' what is going on an'.
INTERVIEWER: yeah and to be involved in this process.
KAMYA: yeah yeah an'.. er all the time she used to ask me how long I have to take this tablet, I said it's for the life time.
INTERVIEWER: Oh!
KAMYA: all the life time used to take it.
INTERVIEWER: Oh!
KAMYA: Oh! So err did I manage to get it, yeah of course you.. manage to get this medicine easily.. because surgery is next to our door.. an' you can get from the surgeries, you can get from the pharmacy I used to take her in the pharmacy in the.. err surgery as well.. so that sometime if **I am** not there.. you.. yourself can manage to do, so in this way I'm jus' trying to.. train her that er you.. become a self dependants.. in future (laugh).
INTERVIEWER: alright.
KAMYA: yeah.
INTERVIEWER: alright and then.. to take the responsibility of..
KAMYA: (at the same time) yeah er..
INTERVIEWER: (at the same time) handling warfarin.
KAMYA: (at the same time) herself yeah (laugh).
INTERVIEWER: yeah. Of course. Errm anything.. else?
KAMYA: that's it yeah.

**5- Interview number 9: Second interview with Participant 2006's parents**

INTERVIEWER: so.. hello… again and I'm very pleased to see you again.. errrmm.. after those months.. errrmm so this time I have only.. a few questions for you.. umm regarding the.. umm dosing and err.. INR.. so could you please let me know how do you feel about the…frequency of INR measurements in.. since the last time we met?
Michelle: errrmmm… well.. i'd been.. various.. so sometimes we phoned up they've gone.. the longest we had was not long ago… which is a 3 weeks didn't.. 'ave not testin' him.. according to the computer.
INTERVIEWER: OK.
Michelle: but… umm.. we tested every week still.. because.. we didn' feel tha' 3 weeks was a good amount of time we were a bi'.. apprehensive abou' tha'.. and [child]… ummm.. was gettin' a li'l bi' ill anyway so.. luckily he stayed in range..
Michelle: bu'.. he was out of range when he was told to take only… an' test in 3 weeks time.. which normally.. we wouldn't do..
INTERVIEWER: (at the same time) I can't remember that we have..
Michelle: (at the same time) he was at 4.6..
INTERVIEWER: (at the same time) we have give him that.. long period.
Michelle: yeah.. he was at 4.6.. and.. he had to test 3 ml.. and test again in 3 weeks time.
Evan: I definitely took that phone call I defini' remember i'.
Michelle: (at the same time) umm..
Evan: an' 've said to Michelle that's far too long.

Michelle: and then we t'.. yeah.. then we phoned back.. bu' w' we tested i' ourselves a' home didn' we?
Evan: yeah.
Michelle: umm bu' tha' was the computer testin' so..
Michelle: the computer isn' good in.. doin' things like tha' so..
Evan: unless (couldn't be heard as mum was talking at the same time).
Michelle: (at the same time) we're alright..
Evan: (at the same time) from.. bein' told on the phone call.. (couldn't be heard clearly).. because his note don't say 3 weeks either.
INTERVIEWER: so could you please rep'.. repeat that again?
Evan: maybe tha'.. because his notes.. does'.. don't say there was a 3 week period of testing.. bu'.. she definitely told me 3 weeks on the phone.
Evan: one hundred percent 'cause as has Michelle e'.. show away..
INTERVIEWER: O'.. OK.
Evan: 3 weeks is far too long.
Evan: so we still tested every week. we didn't ring it through. we were jus' makin' sure tha' he was in range.
Michelle: we did tweek…. a li'le bi' though?
Evan: I think we tweeked one or two days..
Michelle: (at the same time) where it's 2.5..
Evan: yeah..
Michelle: so it's heading quite high a' one poin'..
Evan: (at the same time) yeah. I mean…. when i' comes to the computer.. frequency.. it's.. it's.. no'… as errmm..
Michelle: every week.
Evan: yeah it's no' as consistent.. it can be.. 3 days..
Evan: 2 weeks.. 5 days.. a week.. it's no' consistent.
INTERVIEWER: OK.
Evan: do you know.. where.. where with the human er'.. with the human.. or the consultant.. it was generally test in a week.. test in a week..
Evan: and tha' was in general senses.. tha' we would test once a week.. on a Sunday or a Monday every week and tha' way.. we felt we were.. a lot more comfortable in..
Evan: tha' was more ensuring wha' [child] was bein' in.
Michelle: [child] fluctuates too regularly..
INTERVIEWER: OK.
Evan: yeah.. so the computer wasn'..
Michelle: (at the same time) he is no' a consistent..
Evan: (at the same time) (not heard clearly) consistency enough for me.
INTERVIEWER: yeah.. so it's it's the consistency?
Evan: yeah.
Michelle: yeah.
Child's toy is playing in the background.
Evan: no'.. it's no'.
Michelle: an' the dosage..
Evan: dosage so..
INTERVIEWER: and the doses yeah.
Evan: sometimes it's..

Michelle: (at the same time) the dosage.. was.. silly like.. a' 4.1 he was sittin' a' 4.6 an' the dose was to continue a' **three**..
Michelle: for quite some time.. for us.. that's no' a good dosage 'cause… normally.. if he's a book his so his target is 3 to 4.. so he was already above his target a' 4.6.. we would normally.. alternate.. 2.5 3 for a week period.. an' that's wha'.. the nurses here do an' wha'.. was ourselves would do.
Michelle: bu' the computer came ou' a'.. **three**.. for.. 2 or 3 weeks.. so wha' we 've got told.. so that's quite a length of time an' i' did… go higher..
Michelle: it wasn' a good dosage.. tha' did go higher.
Evan: we have had.. through the computer dosage.. we have had an 8.
Michelle: yeah we ended up comin' in.
Evan: we had an 8.
INTERVIEWER: yeah.
Michelle: because of the computer dosage.
Evan: an' tha' was the computer dose an' tha' was.. testin'.. tha' was… 3.5 test in 2 weeks a' some lon' of tha' an' it was a' 8.
INTERVIEWER: yeah.
Evan: an' he wasn'.. there was no sickness.. no diarrhea.. no vo'.. no illness of [child].. he was eatin' as normal.. an' we had to come here an' have the proper..
Michelle: tha' was two months ago.
Evan: a proper test.. blood test..
INTERVIEWER: yeah.
Michelle: it was in September.
Child making noise.
INTERVIEWER: yeah.
Evan: he was a' 8.. he actually was.. our machine met 8 an' an' i' was 8.4. for a required umm.. an' then… the funny thing was.. it put into the computer.. an' the computer 've said.. to dose 3 ml test in a week.
INTERVIEWER: um no..
Michelle: no it didn'.
INTERVIEWER: it wasn't.
Michelle: no it did not..
INTERVIEWER: (at the same time) it wasn't..
Michelle: (at the same time) it was.. 0.5..
INTERVIEWER: (at the same time) I just checked the record it's..
Evan: (at the same time) 0.5.. ah was i'..
Michelle: (at the same time) it was 0.5..
INTERVIEWER: yeah.
Michelle: but George said.. do no' test..
INTERVIEWER: yeah.
Michelle: at all.
Evan: yeah.
Michelle: but the machine said 0.5 an' then we tested again the next day an' i' hadn' even dropped at all..
Evan: yeah.
Michelle: so George said.. the machine is tellin' you again to do 0.5 bu' we're jus' goin' ignore tha' completely..
INTERVIEWER: yeah.

Michelle: because for [child]'s safety the machine is sayin' 0.5 bu'..
INTERVIEWER: yeah.
Michelle: we a' sayin' as human bein's.. this is ridiculous..
INTERVIEWER: yeah.
Michelle: don't give him a dosage at all.
INTERVIEWER: yeah.
Evan: an' then we don' understand how it works.. obviously i' 3 days later or 2 days later..
Michelle: so.. in that sense..
Evan: (at the same time) so think why.. we tryin' to.. keep warfarin to the system.
Michelle: bu' in tha' sense for a valve.. [child] can' afford to be sittin'.. a' 8.. an' higher..
Michelle: because of.. the thinness is blood goin' an' the pressure puts his valve under.. so he can' afford to be doin' tha' so… I think.. bec'.. in tha' basis.. human bein' person to person nurse to.. nurse to human…. is much better.
Michelle: an' **overall**.. in our opinion… a compu' er.. a computer isn'… wha'.. needs to dose.. a child.. with a valve replacement on warfarin.
Child making noise.
Michelle: because they fluctuate too much.. for a computer to..
INTERVIEWER: yeah.
Michelle: to take that into a consideration.
INTERVIEWER: yeah.
Evan: especially if.. bein' so small.. I think.. tell me I'm no' sure.. we can'.. we are no' able to ring up an' say.. oh he's had a growth spurt.. tha' is gonna… have to go on his up.
Michelle: yeah.
Child's toy is playing in the background.
Evan: when it's.. when we're talkin' to someone it'll go.. you know how he's bein' actually he's been alright he's.. you know.. he's grown a li'le bi' or he's lost a bi' of weight or..
INTERVIEWER: yeah.
Evan: he's no' eatin' particularly well for some reason or another..
INTERVIEWER: yeah.
Evan: he's.. tha' could be a bi' more accountable.
INTERVIEWER: yeah.. we always need er.. you know.. ask for weight but.. we do not want to put that burden on parents..
Evan: yeah yeah.
INTERVIEWER: so that they can go.. er to a clinic and weigh the child..
Evan: yeah.
INTERVIEWER: so.. we always rely on the weight that we have.. but of course.. weight.. you know..
Evan: we can.. we can weigh him if it makes any.. any difference we could weigh him at home.. obviously.
INTERVIEWER: yeah.
Michelle: yeah.
INTERVIEWER: we can take..
Child making noise.
Evan: [child].

INTERVIEWER: it's we can only take a weight when.. once he is in clinic and stuff like that.. ummm.. but for the doses overall.. err it's only.. umm.. the dose is.. is prescribed when the consultant is happy with that.
Evan: yeah yeah.
INTERVIEWER: so it's all the time..
Child making noise.
INTERVIEWER: with all patients.. in the study.
Michelle: umhm.
Evan: (at the same time) yeah.
INTERVIEWER: umm so umm yeah and umm anything else that you would like to add?
Evan: I don' know.. I've jus'.. we jus' prefer when we… when we know we get a.. a dosin' from a consultant who understands..
Michelle: (at the same time) an' I think as well the.. tha' the nurses understand..
Child making noise.
Michelle: tha' parents.. are jus' as responsible for the dosage as.. the clinical liaison nurse an' the consultants because.. we're the ones who see wha' they clinically look like.. because we're a' home with them..
INTERVIEWER: OK.
Michelle: an' you understand your child's condition when you are a paren'.. umm so you know when they're no' lookin' too.. they're lookin' a bi' gippy or.. they're off the food tha' day you can kind o' go well actually he's no' eatin' a particularly grea' amoun' so.. in a fact tha' is goin' to affect his warfarin which 'as an effect..
Evan: mmm.
Michelle: you can.. you can.. mentally start to do it yourself.
INTERVIEWER: yeah.
Michelle: an' I think the nurses take tha' into consideration an' the consultants so.. if you all work on a big team we ge' i'.. spot on every time.. with him normally an' we stay in.. we can stay in range for months can' we?
Evan: yeah.
Michelle: withou' a problem.
Evan: yeah we can.
Michelle: umm..
Evan: (at the same time) an' it's jus' 'cause we..
Michelle: (at the same time) as long as you work as a team.
Evan: we know wha' he's eatin'. we know wha' he's feelin'.. we know.. we can.. we can tend.. generally tell.. if he is.. under the weather an' he's no' feelin' bu' we def' know he's go' a growth spurt obviously 'cause we ge' him dressed everyday if a T-shirt doesn' fit.. it's kind of.. you go' a reason why.. you know.. so we can..
Michelle: yeah.
Evan: we know a lo' abou' him.. abou'..
Michelle: yeah.
Evan: an' if we think.. oh it's been a week you jus' test him there is no'.. he hasn' eaten too much.. you jus' test him an' if it's within range we don' ring in.. it's fine bu' we sometimes..
Evan: sometimes we test three times in two weeks 'cause.. especially if he is… like go' a bi' of diarrhea.. an' we always test then.. we just in case..

Evan: an' we get a bit more cautio' bu' we mean.. we find i' bad me an' Michelle within.. when we have consultant led.. dosage we feel a lo' more comfortable.
INTERVIEWER: alright.
Evan: a lo' more comfortable.
Michelle: ummm.
INTERVIEWER: alright.
Evan: I think just in general we didn'..
INTERVIEWER: yeah.. OK.. umm so.. anything would you like to add?
Michelle: um no no' really jus' tha'.. this this particular way.. isn'.. for [child] I don' think..
Evan: no.
Michelle: like computer..
Evan: yeah.
INTERVIEWER: alright.
Michelle: yeah.. bu' I think.. definitely stick with the.. consultant way.
Evan: I think in the last 6 months.. we've had..
Child making noise.
Evan: a lo' more time was i'.. when out of range.. than we was the **previous** 6 months when it was been consultantly led.
Evan: do you know what I mean that's we we..
Michelle: (at the same time) we've compared i' against tha' haven' we?
Evan: (at the same) we've go' back his book his yellow book..
INTERVIEWER: yeah.
Evan: so we e'.. we try it to.. perhaps bein' part of the pro' this program..
INTERVIEWER: so..
Evan: i' w' good an' then..
INTERVIEWER: so..
Evan: since then.
INTERVIEWER: so during that period when you had.. those errr… INRs out of range..
Evan: yeah.
INTERVIEWER: then you.. said that it was a long interval and you tested it at home why didn't you ring in and said this is.. the INR.. at this time?
Evan: because it.. they told us not to test for 3 weeks.. so we were doin'.. for our for our own med'
INTERVIEWER: (at the same time) yeah but..
Evan: (at the same time) for our own well be'
INTERVIEWER: it would be great for us..
Evan: (at the same time) oh!
INTERVIEWER: (at the same time) to know..
Evan: (at the same time) didn' know..
INTERVIEWER: yes because it would be great for us..
Evan: (at the same time) he was in range.
INTERVIEWER: you know because the.. we are.. recording the INRs especially when it is.. out of range and we try to.. um adjust the dose so we need to know.. after that period of time maybe a few days or.. a week so we need to know **when**.. that INR.. came back to range.
Evan: no he was in range..

Evan: it happens tha' when we.. this is when.. I think one of the only times.. when we've go' tha' time when it's actually stayed.. pretty well we tested we didn' ring in because.. if it 'd been ou' of range we would 've rung in.
Evan: bu' it jus' happens tha' e' e' twice we tested..
Child making noise.
Evan: he was in range. only like a' 3.1 an' then the other time it was like 3 ml so it was only just.. it was like he was.. bu' in range is in range isn' i' so… range is 3 to 4 would e' ring in e' do we
Michelle: when it's been ou' of range we phoned.
Evan: yeah. when it's ou' of range.. we would phone i'.
INTERVIEWER: so we don't.. ring in when he is in range?
Evan: we.. no we we ring in when we are asked to.. like.. if they say test in..
Evan: so when let's say test in two weeks.. we ring up an' if it is in.. tha' normal bu' they si' date was.. don' test for 3 weeks.
Evan: tha' almost..
Michelle: (at the same time) they actually no' often do this.. 'cause he in range for 3 weeks.
Evan: yeah.
Michelle: a' when he was a' his highest bu' then assume when he's a' his highest..
Evan: umm.
Michelle: wha'.. why didn' you ring in.
Evan: we don'.
Michelle: because we were.. we went off the dosage so... for examp'.. I don' know wha' the dose or was a particular time bu' say for example he was 3.7 and the dosage of the computer said… 3 mls test in… 4 days.
Michelle: when we did tha' a' 4 days that's when it was sky high.. so i' i' sent i' really really high.
Michelle: umm…. whereas a dosage for [child].. no think i' 'as 3.5.. wasn' i' whereas as.. if [child] is.. within his range..
Michelle: **our**.. standardised level that we would give [child] and.. the nurses would give [child] would be.. 2.5 3 alternate days for a week.. an' tha' is where he woul' si' quite comfortably..
Evan: (at the same time) generally yeah.
Michelle: (at the same time) an' coast along.
Evan: (at the same time) generally.
Michelle: it's only if somethin' interferes with i' where he is no' well.. or he's 've had a bi' of growth spurt tha' i' will interfere.. other than tha'.. tha' is quite a good level for him.
Evan: [child]..
Michelle: bu' we noticed tha' the computer would give..
Evan: (at the same time) sh sh sh.
Michelle: **different**.. dosages.. a' a therapeutic level.. that's the only difference we noticed.
Evan: umm.
INTERVIEWER: yeah.
Michelle: so.. yeah that's only thing we noticed tha' when he sits within range.. it will give a dosage of like 3.5 test in 4 days.. when really that's no' where he sits comfortably.. he's normally 2.5 3 alternately.

Michelle: we would ‘ve probably seen a more sustainable level..
Michelle: tha’ way.
INTERVIEWER: aha.. OK.
Michelle: bu’ yeah.
INTERVIEWER: I’ve got yeah that umm incident and then the nurses told me.. ummm have let me know that umm you preferred that dose and we went with that and then we..
Evan: (at the same time) yeah.
INTERVIEWER: adjusted the dose again..
Evan: (at the same time) yeah.
INTERVIEWER: umm after that period of time. So it’s just like umm errm we would be very happy if.. when.. you have tested..
Evan: (at the same time) umm.
INTERVIEWER: on your own and then let us know..
Child making noise.
INTERVIEWER: it would be quite.. quite great for us.. yeah.. yeah.. anyway.. umm anything else.. that you would like to add?
Evan: no thank you.

**6- Interview number 10: Second interview with Participant 20010 and his mother (telephone interview)**

INTERVIEWER: hello John.
JOHN: hi.
INTERVIEWER: hello are you alright?
JOHN: yeah I’m fine thank you how are you?
INTERVIEWER: I’m good thank you. I’m very glad to speak to you again.
JOHN: sorry wha’ was that?
INTERVIEWER: I’m very glad to speak to you again.
JOHN: oh nice to speak to you too.
INTERVIEWER: umm so errr.. can you please errr let me know about your.. err warfarin dose and INR.. control.. over the past er six months?
JOHN: it’s been.. rarely bad.. I’d say..
JOHN: yes so.. yeah my INR level ‘as been around.. yeah.. around what.. what it’s… supposed to be.. I’ve never.. (couldn’t be heard clearly)
INTERVIEWER: can you please repeat that?
JOHN: my warfarin erm.. so.. my INR level ups an’ downs ‘n umm.. so i’ hasn’t gone too high up or too far er.. too low.
INTERVIEWER: OK so.. is there any reason behind that?
JOHN: ummm no.. no.
INTERVIEWER: like erm was there any.. err.. change.. in.. diet maybe or… umm other things?
JOHN: no.. no change in my diet.
INTERVIEWER: OK.
INTERVIEWER: so errm.. how.. what.. how do you think about the… erm the dosing and err.. frequency of INRs over the last.. err.. the past 6 months?
JOHN: yeah I think it’s been fine yeah…. yeah.
INTERVIEWER: so erm could you please reflect more on that?
JOHN: sorry?
INTERVIEWER: could you please say more on that?

JOHN: errrrrrmmm….. one..
Grace: (was not close to the phone so not heard clearly).
JOHN: wha's tha'?
Grace: (couldn't be heard clearly).
JOHN: (at the same time) yeah..
Grace: (couldn't be heard clearly).
JOHN: when it's er.. yeah I normally have to check my INR every… two weeks.
INTERVIEWER: yeah
JOHN: so.. yeah.
INTERVIEWER: yeah?
JOHN: yeah.. ya.. umm.. I'd say well.. my….. I don' know how to say i'.
Grace: (couldn't be heard clearly).
JOHN: …jus' tryin' to think.
Grace: (couldn't be heard clearly).
JOHN: no I don' know how to explain i'.
INTERVIEWER: erm so can you.. er.. erm can.. pl'.. Grace can you please come closer to the phone so that I can.. hear you?
Grace: oh he said test i'.. every two weeks.
INTERVIEWER: aha.
Grace: it was you that's it.. that's the large though.. ?? test it it's fine.. it is tha'…….
INTERVIEWER: and and err.. the second six months of treatment?
Grace: sorry?
INTERVIEWER: and how about the second six months.. like the past six months of treatment?
Grace: wha' recheck in six months?
INTERVIEWER: no erm.. sorry.. err.. the INR..
Grace: oh yeah yeah yeah it's been fine yeah.. yeah.
INTERVIEWER: was it OK so erm.. because.. erm er.. John was telling me that it was bad?
JOHN: no I didn' say i' was bad.. I said it was.. balanced.
Grace: he said it's balanced.. it was stable.
INTERVIEWER: sorry?
Grace: it was stable.. within normal range.. where it should be.
INTERVIEWER: aha and.. so how do you think about.. erm.. the frequency of the measurements?
Grace: tha' absolutely fine because he.. he's stable.. he's within normal range.
Grace: it's fine.. it is wha' i' is.
INTERVIEWER: aha and what about the dose changes?
Grace: we haven't really changed on the dose have you?
JOHN: (at the same time) no.. no.. erm.
Grace: so that was fine.
INTERVIEWER: the dose.. the the frequency of dose changes in the past six months?
Grace: that's.. that's you missed her John… but he has been stable.
Grace: 'asn' been really changin' that frequent.
INTERVIEWER: OK so err.. were you happy with the.. err dosing over the.. past six months?
Grace: yes. Yes.

INTERVIEWER: OK brilliant errmm.. so err.. would you like to add anything.. regarding err.. the computer dosing or anything that we have done errmm… in the past six months?
Grace: no.
INTERVIEWER: John?
JOHN: yes.
INTERVIEWER: John would you like to add anything?
JOHN: ….. no I'm fine thank you.

**B- Doctor's interviews**

**1- Interview number 3: HCP1**

INTERVIEWER: So.. umm.. hello again..
GEORGE: Hi.
INTERVIEWER: errr.. thanks so much for agreeing to take part in my research.. err.. the purpose of our meeting is to talk about your experience with warfarin dosing..
GEORGE: umhm
INTERVIEWER: and monitoring before and after using the new warfarin dosing model, so let's first set the dosing model aside for a moment.. err.. could you please let me know about the overall approach that is being used for warfarin dosing and monitoring right from the beginning when the patient starts warfarin treatment?
GEORGE: OK.. err.. that tends to .. a fairly standard initial dose of warfarin that we use within 200 micrograms per kilo.. up to a maximum of about 10 milligrams.. for an initial.. loading dose then we re-check the level.. the following day..
INTERVIEWER: OK
GEORGE: if the level is still.. err.. low then we'd repeat that.. 'n then if it's.. at a reasonable level 'at point we'd half that dose of 200 micrograms per kilo..
INTERVIEWER: OK.. so.. errr.. when do you usually first.. err.. give the first.. the very first dose?
GEORGE: Oh, when.. so.. that's.. pretty much depends.. on the indication.. and on.. errr.. and on the.. the patient's condition..
GEORGE: 'n so it's obviously when they're.. they're havin' enteral feeds 'n we get to know they're absorbing..
GEORGE: so 'at's the first stage.. errr.. secondly.. err.. quite often we'll transition patients from.. heparin onto warfarin..
GEORGE: errr.. so.. again it's sort of.. depending on the clinical 'at we have.. so it's very.. so there's never a set time for that..
GEORGE: it's.. sort of.. very dependant.
INTERVIEWER: so.. that.. let's say.. the overlapping time.. is there like a specific time for overlapping between heparin and warfarin?
GEORGE: err, not really, it's just.. again.. it depends.. on the indication, some patients need to have.. therapeutic.. err.. aPTTs..
GEORGE: err.. constantly, so for example.. patients with mechanical valves.. they're goin' to need constant anticoagulation whereas other patients where the.. the warfarin indication may be not quite so important maybe that's with.. the extra-cardiac Fontans 'n things.. they may not need 'at monitored heparin dose prior to that they may run at that ground level of heparin then transition into warfarin at some point prior to stop when they are able to. The other thing that we need to take into account is this patient having any procedure's stand which may require rapid reversal of anticoagulation, so if

they've got.. trends of pacing wise 'n other things that sometimes change the timing for transition of heparin to warfarin..
INTERVIEWER: umhm.. OK.. and.. how about the target..errr.. therapeutic range.. target INR range?
GEORGE:target INR range.. errr… that's.. **is**.. quite variable.
INTERVIEWER: yeah.. again (laugh)..
GEORGE: (laugh)
INTERVIEWER: this is the.. (laugh)..the issue.
GEORGE: errr…it's errrr… **individual** consultants have previously had.. individual targets that they tend to set for their.. various patients.. but.. we've started to standardise tha' a bit more now so patients.. the volume more common indications we have is those patients with the extra-cardiac Fontan.. conduits..
GEORGE: who attend to have a target INR of 2 to 3.. errr.. patients with mechanical mitral valves tend to have a range between 3 'n 4, patients with mechanical aortic valves tend to have a range between 2.5 'n 3.5.
GEORGE: so.. those are... those are kind of rough areas, but sometimes again we do.. customise that for various patients with various things..
INTERVIEWER: yeah.
GEORGE: we have had patients who've had internal cranial bleeds 'n things like that who we've tar'.. 'n.. particularly.. eer.. that we've targeted lower INRs on, other patients who've had.. **narrow**.. prosthetic valves who we've targeted slightly higher INRs 'n so.. it's not.. it's not.. a.. one size fits all.. usually.. often.
INTERVIEWER: yeah, but.. yeah.. so.. umm.. I was just asking if there are like.. err.. or there should be.. or supposed to be guidelines to.. guide the target INR, the dosing..
GEORGE: there are.. there are guidelines, but… they can be individualised to a certain degree.. err..
INTERVIEWER: OK.
GEORGE: to various circumstances.
INTERVIEWER: OK.. so.. err.. from where can I get like.. a copy of those guidelines?
GEORGE: there is a.. there is a.. postoperative anticoagulation guideline..
INTERVIEWER: sorry?
GEORGE: there's a postoperative anticoagulation guideline on the PICU.. shared drive..
INTERVIEWER: PICU.. OK.
GEORGE: ummm.. then in terms.. I think there is also aeee.. think there is a Fontan guideline but I'm not entirely sure about that.
GEORGE: there's not necessary a hard 'n fast guideline for mechanical valves.. then we tend to use the.. the target INRs suggested by the BNF.
INTERVIEWER: umhm, yeah.. umm.. so.. like.. umm.. it's not specific for the UHL? those guidelines?
GEORGE: errr..not.. generally no.. not all of them anyway.
INTERVIEWER: general..
GEORGE: yes.
INTERVIEWER: so general guidelines. OK, so.. once the patient is.. has started warfarin.. err.. how often do you usually… monitor him let's say.. err.. monitor the INR and change the dose?
GEORGE: you.. you.. to start off with daily.. until.. until we have a sort of steady state over the range that's usually..

INTERVIEWER: umhm, and then afterwards?
GEORGE: afterwards.. it very much..
INTERVIEWER: (at the same time) how often?
GEORGE: depends on the rate of change of the INR..
GEORGE: ummm.. so if you've hit the steady state.. on the current dose.. and you're getting… you're getting consistent INRs on that dose.. you know initially you can have once every 2 or 3 days and then once we're happy.. then if we've got a steady state at that point, I'll drop it down to weekly then two weekly then four weekly. that's my general.. approach.
INTERVIEWER: OK, alright.. and again (laugh), are there any guidelines for it?
GEORGE: no (laugh).
INTERVIEWER: it's done individually?
GEORGE: yes.
INTERVIEWER: OK, and.. then.. err.. the.. increment of dose changing when you have like.. the INR above or below range..err.. when…umm.. let's say.. how this dose is usually changed? and the increment of dose changes?
GEORGE:OK. Umm.. again it depends upon.. err.. both the indication.. for the.. for the warfarinisation and how.. far out of range it is.
GEORGE: there are patients who… you n'.. well known to have.. umm.. very labile INRs.. and in certain situations.. you often find that.. umm.. underdosing then tends to be more a problem.. and then.. you get some pattern if.. you underdose them, they're going low, you have to obviously go high.. it's sort of playing around quite a lot particularly.. that's particularly if you're checking the INRs very frequently..
GEORGE: umm.. patients for example, with mechanical mitral valve.. I tend to be very cautious about reducing the dose on.. too rapidly.. and I'll tolerate.. 'n I'll.. I'll err on the side you keep the INR slightly high as long as there is no evidence of active bleeding..
GEORGE: so if you have had a patient with mechanical mitral valve whose INR of 5.. or.. or 6, you wouldn't necessarily completely stop the warfarin at that dose..
GEORGE: err.. you may want to reduce it down to a.. to a lower dose.. sometimes instead of.. I don' know how often the.. the standard approach with these stop the war'.. stop the warfarin at that dose, we often find 'at we get **a rebound** drop.. then that'll need to be admitted for intravenous heparin treatment because he can't have a.. an.. a lower INR with the.. mechanical mitral valve.
GEORGE: so.. I'll often.. you know.. come down to a very low dose maybe.. a quarter or less of the usual dose.. for a day.. then recheck it and.. you sort of looking to jus' move out of that trough that you get if you actually stop that dose..
GEORGE: obviously, if there is any sign that they.. they've got active bleeding or anything like that, then to stop it and if the INR is substantially high.. like.. over about 6, I'll put even the dose, but..
GEORGE: you know.. tend to be very cautious about jus' stopping the dose for those with very high INRs.
INTERVIEWER: yeah.. umm.. and.. I have like.. noticed on that some.. sometimes when.. when the.. patient.. the patient's INR is just out of the range..
GEORGE: umhm.
INTERVIEWER: errrr.. it's variable again.. like.. some people try to.. I mean some doctors try.. umm.. for some patients, they give.. they change the dose and they give a long interval, but for some others, they do like.. change the dose but with a..

GEORGE: yes.
INTERVIEWER: shorter interval.
GEORGE: (laugh) err.. I think.. umm… err.. I think.. I always I bare in mind that the.. the home INR testing kits do have a.. a range of accuracy to that.. err.. to probably around by about plus poin'.. plus or minus point five..
GEORGE: so therefore if you do have a.. an INR that is very mildly out of range.. again you have to take the clinical.. picture into account… if you've got.. errr.. if you've got a patient who has a Fontan..
GEORGE: circuit.. who's on long term.. who's on long term anticoagulation.. **it's not**.. **a hundred** percent critical where the INR is 2 as a persisting 1.9 or 1.8.
GEORGE: if you have a patient with mechanical valve in… and their INR is very slightly high you got a target of 3 to 4 'n it's 4.1, again.. I'm not worried about that so much. If you have patient his INR erring on the low side he's got mechanical valve then yes I would do something about that, so it's very much take the..
INTERVIEWER: OK.
GEORGE: take the clinical picture in.
INTERVIEWER: aha.. yeah.. so.. what's the reason behind being.. you know.. the patients with valves.. with mechanical valves.. are being more worrying.. err.. than others with Fontan or maybe with err.. than others with the aortic valve?
GEORGE: so.. it's the.. it's danger.. so aortic.. aortic mechanical valves are less prone to getting thrombosis because they got high velocity jets going past them, so the blood..
INTERVIEWER: sorry, high what?
GEORGE: high velocity blood flow..
INTERVIEWER: aha.
GEORGE: so.. the blood flow is faster.. there is less stagnation of blood flow therefore you're less likely to get thrombosis..
GEORGE: on the aortic valve, so which is why the target INR is lower.. umm.. so.. quite often we.. tolerate ee.. we can tolerate the.. the INR going down to two.. two point o (2.0).. err.. on the mechanical aortic valves even though the bottom range is 2.5 sometimes even down to 1.8.. we'll often give low molecular weight heparin to patients whose.. with mechanical aortic valve whose INR dropped a little bit ..err.. as is.. if the.. if the INR is still between one.. still over 1.5 we might give them.. we might give them subcut.. umm.. dalteparin or enoxaparin to target through until we get the.. the INR back up again ..umm.. that's because it's reasonably safe.. err.. to do that.. umm.. the patients with mechanical mitral valves because you've got low velocity blood flow past i'.. and you're entering it's.. potential stagnation of blood flow they're more prone to having thrombi, more prone to having.. mechanical valve..
INTERVIEWER: mm.. yeah.
GEORGE: err.. problems with a low INR, so we're usually very cautious with those most of the consultants would.. admit 'at patient to start an intravenous heparin if the.. if the INR goes below 2.
INTERVIEWER: alright.
GEORGE: umm.. particularly in smaller patients.. err.. so… err.. mechanical mitral valves in.. **infants** are very very high risk group.
GEORGE: err..there is very high.. incidence of valve not functioning getting.. systemic emboli from them as well so that's another group we need to be very very cautious with.
INTERVIEWER: alright.

GEORGE: there's also the group that have the hardest warfarin control as well because.. the… dose change per body weight is such a.. such a fine thing even when you use the solutions tha'.. err.. even a change of 0.2 0.3 of a milligram can be very difficult 'n also administering that.. small dose..
INTERVIEWER: exactly.
GEORGE: makes the.. the error can be mess, so they do tend to be patients with a higher risk as they've got a.. much rather.. a small valve and a small heart and they've got labile.. err.. labile INRs anyway.
INTERVIEWER: OK.
GEORGE: so.. to.. aid avoid the risk of having this thrombosis I think.. it's more dangerous to have a slightly low INR than to have a slightly higher INR..
GEORGE: so therefore, when I'm dosing them I keep that in mind and I tend to.. err on the side of keeping it slightly high.
INTERVIEWER: alright.
GEORGE: and..um.. the other thing is one seen from the point of view of the patients that.. if their INR does go too low then they have to be admitted.. have intravenous access.. have regular blood tests.. it's not very nice for them.
INTERVIEWER: yeah, exactly.
GEORGE: so.. from the point of view of err.. you know the patient.. it's not very (laugh)..
INTERVIEWER: yeah.
GEORGE: OK it's much better to.. if you.. you know.. if I have to choose between a mechanical valve having an INR of 2 'n an INR of 5, I'd rather have 5.
INTERVIEWER: Oh yeah.
GEORGE: yeah.
INTERVIEWER: alright. So.. err.. what are the obstacles that you usually have.. in getting a therapeutic INR and in maintaining it?
GEORGE: err.. so.. umm.. it's very individual for the patient..
GEORGE: some patients will just anticoagulate on a.. a dose of warfarin and I'll stand that dose for.. forever.. and.. you know that they are very very well controlled, you check the INR once a month and everything is absolutely fine..
GEORGE: that.. tends to be the slightly bigger children.. I think they got much more.. they got much more stable absorption.. umm.. the other thing is that it tends to come down if got any bugs and illnesses and get antibiotics.. as..
GEORGE: the younger children.. err.. they can even have quite labile.. err.. warfarin control particularly patients under the age of one.. they are very very difficult.
GEORGE: they use warfarin solutions and.. I think… I think again.. it's very important parents know that they need to mix the solution.. I think.. sometimes you get the impression that in some terms the solution changes as they.. err.. as it settles maybe they're not shaking the bottles quite enough that's important thing to take care about that.
INTERVIEWER: yeah.
GEORGE: sometimes I think administering the.. the same... dose.. when you're talking about a giving 0.2 mls or 0.3 mls again there is a little bit of variability there.. umm.. the other thing is when patients are.. small babies they're on.. formula. Formulas are supplemented with vitamin K.. and that can make it a little bit more unstable as well but not difficult to treat.. umm.. other more things that happen are small children frequently get **bugs**.. and.. they frequently go on antibiotics, so if they get a bug.. particularly if

they get vomiting and diarrhea, the absorption of warfarin goes down and.. then also if they are on antibiotics then.. the.. antibiotics change the liver enzyme metabolism.. ‘n ‘erfore the INR changes as well so it can either reduce or inhibit the liver enzymes that for you get instability that way.. so we quite often find patients who give a leap above their INR it goes.. it goes out of range for a few days then it comes back again , bu’ see you kind of need to see more their.. their usual background ranges and see what’s happened when the.. when they notes to have that.. it’s pretty much.. (laugh)
INTERVIEWER: (laugh) yeah… so.. and..
GEORGE: and we ‘ve had.. we’ve also had some patients we get particularly teenagers who.. where compliance with taking the medication… we can never know for sure.. bu’ we think that has been an issue in those patients as well, so.. again you sometimes get these patients who… you think probably don’t take as much as tha’ been prescribed..
INTERVIEWER: OK.
GEORGE: or don’t take it at all or miss some doses or intimately miss doses then.. their INR control tend to be extremely difficult.
INTERVIEWER: umhm. OK and of course you have already mentioned the problem with the mechanical valves and those patients on.. yeah.. of course.. definitely those are more difficult than others. Alright.. so.. umm.. now.. errr… errr.. we go to the model.. the new warfarin dosing model, so could you please tell me about.. your experience so far with this new dosing..
GEORGE:(at the same time) I mean I think..
INTERVIEWER: (at the same time) algorithm?
GEORGE: day to day.. maintenance I think it’s.. pretty good, it’s.. you know.. I’ve.. I’ll look to the doses that it gives and.. I’ve.. rarely seen any tha’ I.. disagree with I think it’s.. quite good I think what.. the model **doesn’t**.. do is it doesn’t have that.. that kind of **bias**.. in it so they have.. I think the only times I’ve ever… disagreed with the doses have been those patients where.. umm… you **definitely** don’t want ‘em to go low so you go to a slightly higher level.. and the model minus a’ all give this much ‘n I’ve.. ‘n I’ve seen that dose not enough gone.. I think if we give that there is **a danger**.. that it might drop below range and I would rather.. come down more slowly and stay in range.. I pro’.. you know tolerate staying in the.. slightly high area than.. come..
INTERVIEWER: OK, so this is.. when the INR is on the lower range or.. or below..
GEORGE: this is usually when the INR is in a higher range..on the patients where you don’t want to risk it going too low..
GEORGE: I think sometime’.. you know.. it would be fine if it’s a patient who can tolerate having a lower INR..I wouldn’t have a problem with the dose that it’s suggesting… bu’ think in these patients where lower INR would be more risky..
GEORGE: umm… you .. you kind of.. you bias your.. what I tend to do is ‘at I tend to say.. rather to get a lower range I’ll probably do this.. ‘n err.. maybe.. yeah I don’.. ‘n jus’ say.. so come up a little bit on what I suspect…**we need** .. ‘n then tolerate having that slightly high INR for longer.. to see if it come down more slowly rather than trying to get back to the.. err.. into the middle of the therapeutic range ‘n then overshoot ‘n end up.. having too low, so I think that’s really been in times ‘n the other things maybe sometimes those.. err.. there’s other things where you need jus’ apply a little bit of judgement on children who are.. **unwell**..
GEORGE: who.. you know.. you might think.. OK.. what’s goin’ to happen when they.. they are unwell.. when usually that’s the case it’s jus’ monitoring ‘n see what happens.. umm.. I was… I’m no’ a hun’re’ (hundred) sure about how the… timing of the..

rechecking occurs because ‘at dose and ‘en the.. the model doesn’t provide.. the intervals for checking ‘e INR..
INTERVIEWER: no, it doesn’t provide intervals so it depends on.. my judgment..
GEORGE: yeah.
INTERVIEWER: my personal judgment again.. and.. err.. I try to follow what the doctors’ judgement..
GEORGE:(laugh) right.
INTERVIEWER: I see.. you know.. I try to compare with those who are on the.. you know.. doctor dosing and see how frequent is the monitoring and again depending on how stable is the patient and then I decide the.. the interval, but sometimes again I get like.. maybe.. a doctor that .. doesn’t agree with this..
GEORGE: yeah.
INTERVIEWER: interval either making.. well mostly doing it on a shorter interval..
GEORGE: umhm. I mean I.. I..
INTERVIEWER: (at the same time) I’ve got that incidence.
GEORGE: I try to extend the interval to as long as I can because I think.. umm.. if you measure a transitional INR… it’s OK as long as you.. realise that it’s a transitional INR it’s not goin’ to be.. where you’re.. you don’t.. you don’t react to it too much. ‘n I think sometimes it’s useful to do.. short term INRs to see.. a sort of a rate of change.. so you can kind of see where things.. err.. where thing are likely to head ‘n if your.. if your rate of change is too high then it might make you come up a little bit on the next dose.. err.. bu’ I usually.. if I do a dose change I’ll usually try ‘n leave it a’ least 3 days before rechecking ’n that’s the thing as a.. danger…….
INTERVIEWER: sorry.. err.. could you please repeat that again because I think I’m not getting you..
GEORGE: OK.
INTERVIEWER: exactly?
GEORGE: so if.. if you have sort of a high INR.. and you.. you want to check.. you change the dose ‘n recheck it.. umm.. sometimes I… the when you recheck it’d be a difficult question..
GEORGE: because if you do.. er.. if you do a large dose reduction, you won’t see the… result of that dose reduction until around abou’ 48 hours after you’ve done i’, so therefore the argument is that you should really be checking the INR the following day..
INTERVIEWER: OK.
GEORGE: now.. some people.. for whatever reason.. we observed do have very rapid change their INR ‘n response to doses ‘n they will change within 24 hours I think sometimes.. although that’s not the **destination** where the INR is goin’ to be when you recheck in 24 hours, it could sometimes give you.. if make sure abou’ how quickly the INR is dropping ‘n response to what you’ve done..
GEORGE: err.. so if you do see a very rapid drop when you reduce the dose somethin’ ‘at might change your… way you’re going to put your next dose to sort of.. instead of coming down very steeply you come down in a more shallow fashion.
INTERVIEWER: yeah.
GEORGE: umm.. bu’ sometimes you know.. you know it’s not changed at all ‘n then.. the temptations to come down even lower.. bu’ err.. you do avoid that.. so.. it’s a very… it’s a dark art (laugh).. so..you know.
INTERVIEWER: yeah, it is quite tricky we.. we do have some people.. some patients like..err…err.. they have a rapid.. very rapid drop of the INR within 24 hours..

GEORGE: yeah.
INTERVIEWER: so.. yeah.. this is another.. problem.. so..umm.. has this err.. new computer dosing had influenced your overall approach to warfarin doses.. dosing?
GEORGE: how I prescribe that.. I don't think so (laugh).
INTERVIEWER: (laugh).
GEORGE: I think I've always stood what I've done but err.. you know.. I think the.. I tend to find that the computer doses are.. are sensible.. I mean it's just like.. err.. er.. I think I've never seen any that 've been absolutely crazy.. umm.. I think I would sort of trust it to do much of.. much of the warfarin doses in patients who.. **don't have**.. **additional** sort of complexities about.. about what's going on I think sometimes you get a patient who got very labile doses.. as long as you have an experience place in prescribing i'.. I think.. probably 'at might be slightly.. more reliable because we've got to take a lot of.. err.. **additional** factors into account that I think probably the.. the warfarin dosing model doesn't.
INTERVIEWER: yeah.
GEORGE: umm.. so.. I think it's the.. all of those extreme of things like.. you know… these patients who.. who do have the.. who are a' higher risk because you know this patient has a mechanical valve that isn't functioning well.. therefore you got to be extra cautious about not dropping the INR too much I don't think you can.. program that into the model the model will always do what it.. what it says, more of those patients who are havin' that's very.. that's very up and down doses you may want to.. tolerate the INR going out of range just to stay on a consistent dose for a while..
GEORGE: umm.. I think sometimes you may want to **start over**.. over-treating those oscillations … err.. in INR.. umm.. rather than jus' trying to actually find out what's happening in the steady state.. think those are the only things bu' I think gen'.. by in large it's.. it.. does pretty much what I would… I would do I think.
INTERVIEWER: umhm.. so.. err.. umm.. would you please comment on any advantages or disadvantages of this computer dosing? depending on your experience so far?
GEORGE: I think the computer dosing most advantage that the.. it turns around probably a bit faster.. for the patients.. you know.. umm.. if.. err.. at the moment.. you know.. the.. the system is that the parents call in the INR..
GEORGE: err.. one of the liaison nurses takes that down 'n they have to find a doctor to prescribe it.. I think.. if you can cut that stage out.. uhm pardon me.. err.. then that'll be a lot faster 'n then I.. I can potentially see the person calling up 'n.. 'n getting the result or.. even makin' the.. the system available to the patients so that they can jus' directly input what the INR is 'n then get a dose.. back out again..
GEORGE: obviously with.. safety parameters that if the it's out of range then they should… contact simply bu' I could see that being a.. a much.. much easier for the.. for the patients to use potentially..
GEORGE: umm.. I also think.. sometimes.. err.. I could say.. I think.. sometimes some of the doctors **over-treat**… the slightly high slightly low results and tend to **not**.. have the idea of what's happening with tryin' to smooth everything out.. umm.. I think that's.. sometimes people have tha' reaction tha' they over-treat these.. these circumstance it could be potentially better for that.. ummm.. bu' I would.. I would say that it would need be careful… oversight 'n if there is ones that are just.. aren't settling or those higher risk patients I think it might be better.. being done in a.. err.. with more.. clinician input.

GEORGE: so I think.. I think maybe a combined approach with the higher risk patients having a computer suggested dose.. bu' then saying.. agree or disagree with that 'n havin' the ability to override that then that'd be better.
INTERVIEWER: great.. umm.. and the disadvantages?
GEORGE: err.. disadvantages are.. just the potential to like have those.. situations where.. you would change things jus' the clinical picture not being taken to.. to account I think that's probably the.. the biggest.. the biggest difference.. umm.. yeah.
INTERVIEWER: yeah, alright.. so would you recommend.. umm.. the warfarin dosing model or the computer dosing.. err.. to other clinicians in the same.. situations?
GEORGE: I think so yeah, I think it's very useful yeah.
INTERVIEWER: umhm.. brilliant.. umm.. err.. OK.. so do you have any other comments..
GEORGE: err.. no.
INTERVIEWER: that you would like to add?
GEORGE: no, I've said everything.

**2- Interview number 4: HCP2**

INTERVIEWER: umm.. hello.. thank you very much for.. agreeing to take part in my research.. umm.. the purpose of our meeting is.. to.. err.. talk about your experience with warfarin dosing and monitoring.. err.. before and after using the warfarin.. the new warfarin dosing model.. err.. so.. err.. first let's .. err.. set the.. err.. warfarin dosing model aside.. and err.. could you please.. err.. let me know about.. err.. the overa' your overall approach that is being used for warfarin dosing and monitoring umm.. right from the beginning when the patient **first** start.. starts warfarin?
SARAH: err so.. thank you for asking me to participate.. err.. usually.. we start the warfarin **mostly** post-surgical.. so it's usually in the intensive care unit or on the ward as a transition from warfarin so if we want to put our patient.. on warfarin usually we start with the heparin infusion and gradually introduce.. the dose and overlap till we achieve our INR target then we stop the heparin.
INTERVIEWER: umhm.. so.. errr… what about.. er.. the dose the first initial dose and how the.. target therapeutic range is decided.. err.. are there any guidelines for that?
SARAH: er.. so it is depend on the underlying diagnosis so.. and the difficulties during surgery and.. the size.. of the patient and for example the artificial valve so there is err.. and the cardiac function. So usually there is a general consensus.. regarding what we give for the mitral valve.. what if the valve put in a **smaller** than usual or impaired function.. we increase our target.. err.. aortic valve the **same** usually it is a **less** of an INR range than the **mitral** valve but if the cardiac function if is impaired or the valve is too small.. err.. for the patient we try to **allow** for more.. err.. a larger.. err.. scope.. there is different ones for.. err.. obviously the Fontan circulation.. where we maintain a lesser INR er.. range… and.. ummm… those are the main really indications... are the left-sided valves for the **right**-sided valves.. it is a new evolving era with the adult congenital tissue valves and the valve 'n valve.. err monitoring… but going back er to the children.. we find that children below 2 years are **extremely** difficult to **monitor**.. their INR 'n sometimes we resort to long term subcutaneous heparin instead.
INTERVIEWER: umhm.. so.. err.. are there any.. like.. guidelines.. errr.. documented somewhere..err.. for..

SARAH: for the dosing we have a general.. er.. guideline as for the dosing.. and.. umm.. and it's the experience of the unit.. and… err.. there is a documentation of a consensus between professionals.. on what.. we expect within our unit for our patients it's difficult to… errm… to… standardise that all over the country but **most** of the guidelines are based on.. err.. err.. experience.. err.. somewhere else and our own experience so it's a combination.
INTERVIEWER: aha.. alright.. and.. err.. how do you usually first start dosing of warfarin?
SARAH: so we start with 100 to 200 mics.. err.. per kilo.. as a starting dose and then we build up gradually as per INR.. err.. an'.. err…. and it is depending if there is ongoing bleeding pos' surgery and there is other concerns.. but usually till we build it up we cover with therapeutic doses of heparin.
INTERVIEWER: umhm.. so.. errr.. is there any specific time for overlapping between heparin and warfarin?
SARAH: usually it takes about.. er.. 4 days to a week for the warfarin to produce the target INR.. er.. and.. we s'.. we usually stop our heparin depending on our target so if we.. our target is 3 and we achieve a target of INR of 2.. we stop at that.. err.. stage and then carry on upgrading the.. the warfarin.
INTERVIEWER: aha.. so.. how about the frequency of the INR measurements?
SARAH: it's usually once **a day**.. however if they have concerns.. and… the patient is bleeding or we are not achieving the target we use it by the machine and if we are not happy with the machine we do a blood sample to compare.. and the other thing is if there is **sudden**.. er.. err.. unstability of the INR measurement either too low or too high..
SARAH: we re-look at the machines and see if it had been standardised.. and then we do a lab blood sampling.. but we find with young children less than 2 years.. it is extremely difficult to control their INR.
INTERVIEWER: aha so this is at the beginning of treatment it's done daily.. and so.. how about when… later on?
SARAH: well it's depending if.. there is a group of patients who have very stable INR and you.. do them every 4 to 6 weeks and there is patients that still.. wa' need er especially the children remain a concern on the long term..
INTERVIEWER: umhm. SARAH: they need at least twice weekly or once weekly.. er.. measurement.. with frequent admissions.
INTERVIEWER: alright so.. what are the obstacles that you usually encounter in obtaining and maintaining a target therapeutic.. INR range?
SARAH: it is the unpredictability in children for the… er we don't know is that it is the liver metabolism or pharmacokinetics in children.. that prevent them from.. err.. either they over.. er.. metabolise the warfarin or they retain it.. err.. so…. it is a quite unstable group.
SARAH: that we haven't been able to scrutinise what is… the reason of the unstable INR but the grou'.. those patients.. er.. the infants and patients up to 5 years.. are a big problem in INR control.
INTERVIEWER: aha.. so… yeah.. so those.. this regarding the age infants and up to 5 are there any.. umm.. other.. risk factors let's say.. that .. err.. contribute to the **instability** of the INR?
SARAH: well it could be the..  the frequency of infection the requirement for antibiotics.. the regular change in diet with unpredictable response.. er.. of the INR to

that.. er.. which includes.. err... **unknown** factors.. err.. we usually give the families a list of things to avoid..
SARAH: but still.. it doesn't always.. work out but with infection and antibiotic there is consistent.. er.. derangement of the INR that.. we usually try to.. to be aware that they will be increase frequency of **testing** during that period.
INTERVIEWER: aha.. alright.. and how about the.. err.. the indication those with valves and those with Fontan.. err.. is there any.. err.. like.. err.. do they differ in their.. err.. stability of INR?
SARAH: well it's depending Fontans with stable liver function and.. err.. especi'.. err.. the non-failing Fontans it's again it's a difficulty because the liver metabolism.. err.. is is.. err.. is very unpredictable and abnormal but stable Fontans.. usually have a reflect on a stable INR again it is the diet and the other infections that.. may destabilise things but... most of the Fontan population is.. er.. stable in that regard especially as they grow older.
SARAH: err… err.. but the.. the patients with difficulties are the young patients who needed mitral valve or aortic valve replacement are the main concern.
INTERVIEWER: aha.. alright.. err.. so yeah.. umm.. it's just like.. err.. during my audit or my usual work with wa'.. with the warfarin dosing.. er.. the.. er.. I sometimes see that when patients are.. let's say.. just out of the range.. err.. so some doctors tend to.. for some patients tend to give like.. change the dose and give longer interval but for some other patients they tend to do.. a more frequent.. INR.
SARAH: yeah we do that because.. the patients who are stable.. errr.. and… there is.. no conce'.. for example we are more lenient with.. the Fontans because there is.. er.. no immediate risk.. if they drop significantly on the.. conduit but.. with valve especially mitral valve.. we become very anxious if there is.. a change.. a significant change in the INR.. so we test them more frequently so we tend to test the valves more frequently.. errmm.. and less frequently so if the Fonta'.. for the Fontans.. and if they need **changes**.. we.. and and.. we what we look we look at the whole profile of the previous..
SARAH: err.. err.. their.. err.. tendencies.. so some patients again it's become individualised.. that they are stable over a long time so you don't need to to test them very frequently.. and some patients they are just very variable that you can not trust.. that if you go' give them a longer period that they will have err… a stable INR.
INTERVIEWER: alright.
SARAH: so it is just on the case.. there is no rule to it it's just goes by case on case.
INTERVIEWER: aha.. so.. errr.. is there any specific reason of why those patients with valves being **more**.. risky?
SARAH: the patients with… the ones who have valves are more risky because.. if they drop their INR and we have given them a long period.. and we haven't tested them or checked them.. that the valve will **clot**.. and then this means urge'.. you know risk of sudden death.. as.. urgent need for surgery so we can not afford to leave them for a long times.
SARAH: especially in young children with unstable INR.. so more of grown up children 10 years onwards and young adults.. usually they have more stable INR unless they have a major infection.. or a major problem.. but the.. the young children they very unpredictable so we can not give them a **blanket**.. of non testing or long testing or automated testing.. in couple of day.. err.. in couple of weeks we can not afford to do that.. because they are very high risk.. especially the small valve.. in the mitral position.. is very high risk so it is not like the adult mitral valve.

SARAH: so it is not like the adult mitral valve.. ‘n usually in small children they use inverted aortic valve.. with unpredictable behaviour.. so that’s why they need higher INR range and frequent testing.
INTERVIEWER: alright brilliant.. umm.. so.. errr.. now we can.. err.. we come to the.. er.. the new warfarin dosing model could you please let.. me know about your experience so far with this.. new.. dosing.. of warfarin?
SARAH: so the new dosing with warfarin we find it useful **in**… in.. in the older children.. that’s finds usually consistent and no problem.. we finding it **difficult** to.. **rely on**.. and we always have to question.. err.. in younger children because it it sometimes… it is not **aware** of the clinical background so yes that’s a mitral valve it should be 2 to 3 but it doesn’t take in account why we change that because maybe we happen to do a scan.. and the cardiac function is impaired… so.. or there is arrhythmia.. so we want to have higher range during that period.. just to **cover**.. that high risk period before we go back.. or you give a period ‘n ‘e you say OK we’ll derange very quickly.. as sometimes the parents who are used to **dosing** with frequency sometimes they are not **happy** to adhere with it.. and they want to **change** it more frequently.. umm.. and there is… few but important incidence where longer.. errm… recommendation.. err.. might have.. resulted in.. the fact that.. the INR went very high and we didn’t test it early enough or too low.. so we **still**.. have to take a bit of a part of control in the younger population.
INTERVIEWER: aha.. so.. yeah.. umm so could you please let me know about.. you know.. the.. advantages and disadvantages that.. er.. you may think.. with with this.. err.. is associated with this.. err.. dosing model? So we have got this.. umm.. err.. that it doesn’t take into account the clinical situation are there any.. err.. advantages or disadvantages? For this.. er.. model?
SARAH: hhh I think the advantages it will **work** for certain groups very well ‘n it will help with that.. but it still that model have **not**… helped us with the young groups because.. it **still**.. have.. I don’t think it have worked out…. **why** that particular group.. err need more frequent.. dosing it **still**… it still not **happy** to.. to give them the frequency that we need.. so you end up.. with **a blanket**.. dosing.
INTERVIEWER: yeah.
SARAH: so I’m not sure I want to know from you.. have we taken in account the pharmacokinetics in the very young..
INTERVIEWER: yeah..
SARAH: infants?
INTERVIEWER: it takes into account the pharmacokinetics **and** the pharmacodynamics but it doesn’t give.. err.. the interval or the time for the next INR checking so this again depends on.. err.. on the.. err.. our..
SARAH: clinical?
INTERVIEWER: yeah.
SARAH: so and and that’s why the clinical factor have to look at that and say OK.. this is what the automated thing.. does and this is what we usually deduce what the automated decision.. then we say.. OK yes we are happy with this or no.. we have assessed this patient today and we are not exactly happy we’ll just test a bit earlier.. or give a different dose..
SARAH: so we look at the dosing first.. that given the automated doses.. and then… s’.. assess yes we agree or not.. so there is still a clinical input that is important.

INTERVIEWER: so you are.. errr.. so your main concern.. is it the dose.. or.. the interval?
SARAH: sometimes both.
SARAH: so sometimes both because… OK.. sometimes we put the target.. and then.. during.. or.. depending on the clinical situation we change our target OK my target was 2 to 3.. but something now happened the cardiac function is more impaired..
SARAH: or there is.. he out grown his size.. or there is a patient.. **valve** mismatch.. and I decided that I will increase my target and I want to test him more frequently..
SARAH: so sometimes the clinical situation.. will change.. what.. the automated decision based it on.
INTERVIEWER: aha.. so do you mean that.. err.. changing the target is like.. err.. temporary.. temporarily?
SARAH: sometimes yes change the target temporary because there is an acute change in the situation.. then when it resolves you go back to your.. previous target.
INTERVIEWER: yeah and again we can do that with the.. err.. you know.. with the automated dosing..
SARAH: yes..
INTERVIEWER: so we can put that..
SARAH: yes we usually.. we put a note that please change the target.. and change the dose..
INTERVIEWER: alright.
SARAH: and.. most of the time.. there is OK many occasions that… they show you the dosing.. errmm.. and then you say OK I.. I'm fine I'm happy with it.
SARAH: so we don't always we reject the dosing… most of the time it works.. but there's.. **certain** groups that we request… that… we want to know what's happening with the dosing so we just.. keep… on top of it.
INTERVIEWER: aha.. OK. So.. err.. at the moment with the two groups of people who... the indications for warfarin.. the long term warfarin are those with Fontan and those with valve.. err.. so which group do you think that the.. automated dosing.. works better?
SARAH: … for most of the Fontans.. err.. it works OK because usually we do our Fontans four years onwards.. with the slightly younger Fontan and that's why we stopped giving it for Glenns because they are very young and it's difficult.. to warfarinise them we'll rather put them on aspirin..
SARAH: so.. err.. it works for.. the older valves…a'.. and the older Fontans.. it works fine.
INTERVIEWER: aha so you think it's it's mainly.. the main concern is the age?
SARAH: the age group.. yes.
INTERVIEWER: aha. Alright.. umm.. so.. umm..
SARAH: the age group and the cardiac function.
INTERVIEWER: exactly.. umm.. so.. err.. would you recommend this dosing model for other clinicians in the same circumstances?
SARAH: .. err.. you mean in congenital heart disease?
INTERVIEWER: yeah.
SARAH: I think.. it is it is it is a useful model.. it is just we need to.. err… reach the consensus of the flexibility of the model..
SARAH: so once the model is flexible to accommodate the **much** younger group that needs more.. frequent dosing.. I think it should work OK.. but as with automated

things.. I I think with.. our complex patients.. there has to be always a degree of judgment clinical judgement.. and input..
INTERVIEWER: yeah.
SARAH: it.. can not be just.. an automated.. err.. service.
INTERVIEWER: alright.
SARAH: because the result of unpredactabilities.
INTERVIEWER: yeah exactly.. um.. so.. umm… do you have.. err.. any recommendations regarding this.. err.. model?.... so to make it.. work better?
SARAH: …. I'm not sure what will work in that model from a mathematical point o' view so if a patients is.. for example if we take a patient who's very unstable who needs **frequent** testing.. and frequent **dosing**..
SARAH: would.. the model re-adjust that particular patient?
INTERVIEWER: err.. so.. er.. umm.. if w' umm... as much.. err.. INRs as we get.. so the better.. it will predict so.. err.. the more the INR input into the model the more it will be able to.. **adjust** the dose.
SARAH: so.. understand the profile of the patient.
INTERVIEWER: yeah.
SARAH: so you can.. you basically can **individualise**..
INTERVIEWER: yeah.
SARAH: each model..
INTERVIEWER: yeah.
SARAH: you know **tailor** it..
INTERVIEWER: yeah.
SARAH: to each patient..
INTERVIEWER: yeah.
SARAH: that particular patient..
INTERVIEWER: yeah.
SARAH: with the.. it is pharmacokinetics.
INTERVIEWER: so this is what we are doing at the moment..
SARAH: yeah.
INTERVIEWER: we are taking the INR histories for those.. err.. for those starting warfarin for the.. err.. who are **stabilised** on warfarin.. so we take.. err.. their history of INRs for a specific per' period of time.. so the model can predict the pharmacokinetics and pharmacodynamics for that specific patient.. err.. and then.. will be able taken into account target range and the baseline INR.. and.. errr.. so it will predict the dose for that patient and.. once we.. err.. as more as we can get from the INRs we update that.. so.. it will be like **updating**.. err.. whenever we get a new INR.
SARAH: so we have to look into the over result and.. the success rate and the failure rate and.. the maybe the rate where.. it had to be.. errmm… individually re-adjusted or didn't agree and then we will **know**.. how much this model fit.. in a scientific… numbers.
INTERVIEWER: aha. And for those people who are starting for the first time we are doing a genetic test for them.. for the enzymes involved in metabolism and the enzyme VKORC1 the vitamin K epoxide reductase to see.. how sensitive they are to warfarin and we are using that **as well**.. err.. for them.. to predict their warfarin doses.
SARAH: OK so it's this will deal with the rapid and the slow metabolisers
INTERVIEWER: yeah yeah so.. this.. this is our..

SARAH: because this is one of the.. other.. difficult problems is is.. err.. the.. the rate of the metabolism as well.. ‘n who is a fast metaboliser ‘n who is a slow one.
INTERVIEWER: yeah yeah alright.. err.. do you have any other comments?
SARAH: no no.

**3- Interview number 7: HCP5**

INTERVIEWER: hello.. and thank you very much for agreeing to take part in my research.. err the purpose of our meeting is to.. talk about.. your experience with warfarin dosing and monitoring.. before and after using the.. new warfarin dosing model. Err.. first of all I would like to.. err.. talk about thee overall approach.. err.. that is being used for cur’.. currently for warfarin dosing and monitoring.. umm could you please let me know about that.. right from the beginning when the.. patient first start.. warfarin treatment?
TAJ: err.. I mean we have been dosing.. on alone.. with the.. intermittent obviously intermittent sort of… erratic INR.. changes.. with this WATCH study…most of the time.. I feel that it is.. **in**consistent with what we are prescribing..
INTERVIEWER: um sorry.. I just need to know.. first.. the.. **usual** practice.. in warfarin dosing and monitoring like.. when the first.. when you first start.. dosing the patient.. errmm.. the INR.. the target INR range.. those stuff.. right from the **beginning** of.. of warfarin treatment.
TAJ: ya so.. we.. have different INR.. sets for.. different.. sort of.. diagnosis..
TAJ: for valve.. and e’ if it is like mitral valve we normally keep.. more than 2 or 2.5 to 4.. err similarly for aortic valve we have slightly.. err.. **less**.. umm INR reading.. acceptable.. and.. the other commonest.. umm sort of.. err warfarin prescribing is for.. univentricular heart this Fontan post Fontan.. and that is again has a.. **big** range accepting anywhere from 1.5 to 3 depending on.. sometimes.. err.. different consultants’ preference… so.. in general.. when we **start**… aiming that INRs will start with a sort of.. **loading**.. dose.. of is.. which is 200 microgram per k g (kilo)..
TAJ: **normally**.. I prescribe within.. that range.. sometimes we have to give that dose.. err few days… while patient is in and observing.. to get to the.. target INR.. and err.. yeah we start monitoring **from**.. **day**.. one.. after giving.. that dose before we end up having.. maintenance dose.
INTERVIEWER: so and er how about the um the that period of overlap with heparin… how long?
TAJ: e’ e’ it’s normally 2 to 3 days.. as minimum.. er when we start… mmm soo and sometimes.. as I said it takes.. even longer.. err because few patients.. like in my experience last one.. we gave him.. same two poin’ er 200 microgram per k g (kilo) per dose.. but.. next day.. even we had.. to go even higher.. which was nearly 300.. microgram.. err and still we did not achieve INR until fourth day.
TAJ: the target INR. So sometimes it is prolong.. but normally we do get to the INR on.. second day or third day so 3 days of overlap.
INTERVIEWER: alright. So umm.. are there any guidelines for.. err.. you know.. starting.. the starting dose.. the target INR range.. umm the time of overlap with heparin are there any specific guidelines for.. for these things?
TAJ: …. Ah.. I’m not fully aware of.. of any guideline.. but I.. what.. I’m aware of is the practice.. here.. which is err as I said.. starting with 200 micrograms and then going to hundred microgram..

INTERVIEWER: OK.
TAJ: after 2 days.
INTERVIEWER: OK. And the target INR..
TAJ: (at the same time) target INR..
INTERVIEWER: (at the same time) range?
TAJ: again varies between.. the different diagnosis.. sometimes it is accepted as low as 1.5.. for.. er.. Fontan patients.. where we have low risk of.. for v'.. valve and mechanical valves obviously more than 2. So once we get to more than 2.. normally we stop err..
INTERVIEWER: so what's the reason behind those people with valves.. getting.. higher target.. range?
TAJ: …. Err.. er.. there is **more** risk of clotting.. in those mechanical valves.. especially **low** pressure valve which is mec'.. umm mitral valve so that's why the risk of err.. you know..
INTERVIEWER: so er could you please clarify what you mean by low pressure valve?
TAJ: err.. where.. we have er.. umm the press'.. the.. mitral valve.. where blood flow.. from.. left atrium to.. right ventricle (I think he meant left ventricle).. the.. thee.. thee.. flow gradient or flow velocity is much low.. so there is more stasis sort of thing.. e' e' it is not stasis but the flow velocity is less so blood is not rushing.. so there is more chance of er.. stagnation.. there is more chance of.. having clot.. in that valve.
TAJ: err.. comparing.. mitral valve to aortic valve.. aortic valve again.. when blood is ejected it's a high pressure.. sort of ejection from the left ventricle which is.. if we compare.. it is hundred m m h g (mmHg) versus.. 5 to 10 m m h g so that is.. a comparative difference.. so e' e' it's less chance of clotting or stagnation… on er.. on.. .. on er mit'.. on aortic valve compared to mitral valve.. so that's how.. we.. determine.. a higher INR.. ratio for.. those valves mechanical.. mitral valve.
INTERVIEWER: alright.
TAJ: and err.. similarly.. umm..in in Fontan.. again.. there.. there is there isn't any mechanical valve kind of thing.. it's just the slow movement or stagnation of blood.. so you are just pre-empting.. sort of.. so that's how you.. accept.. relatively lower INR or lower thinning.. for definite valves.
INTERVIEWER: umm.. so umm.. how about thee **frequency** of INR measurements the monitoring?
TAJ: yeah.
INTERVIEWER: at the beginning and then afterwards?
TAJ: for mitral valve.. we do very frequent INR monitoring.. and simple reason being.. there is more risk.. so we just don't want to.. er.. we want to avoid.. any sort of low INR situation.. hidden.. so that's er.. but ideally.. err.. e' two weeks… one to two weeks is.. acceptable sort of monitoring for mitral valve..
TAJ: e' if we have a stable INR situation.. but sometimes while we are still achieving a therapeutic or stable INR situations we do… relatively 2 to 3 days or.. quite.. regular monitoring.. especially when the patients are jus' started on.. or newly started on.
TAJ: for.. a Fontan sort of thing.. since we have a big range acceptable range… from low to.. so.. we monitor three weekly or four weekly.
TAJ: .. and er.. very rarely we.. get to surprised that.. er.. in four weeks.. we… get.. you know.. e' e'.. erratic reading… in terms of high or low.. so normally we get.. you know.. er.. sort of stable reading..

TAJ: even before er.. a four.. four weeks' or three weeks' monitoring.. with the.. umm.. er.. if we have a.. big acceptable range.. for er.. for an aortic valve.. normally two weeks.. is quite acceptable.
TAJ: although in practice we had to do… relatively sooner.. because.. because of this population… you know.. where you.. have some unseen things like diet an'… for for kids and these things..
TAJ: intercurrent illness.. sometimes.. they are on antibiotic or.. even.. infection so… that is.. that determines their… you know.. intermittent… err change in the.. follow up or frequency of err.. INR checking.
INTERVIEWER: umhm so they usually umm..
TAJ: one to two weeks.. is quite acceptable or quite.. er.. in practice.. for um.. aortic valve.
TAJ: … err.. for mitral valve I would say… we.. aim to.. do two weeks.. in most of the situation but…. in practice rarely we get to that.. so we have to monitor.. relatively sooner and that is simply because.. mitral valve nobody would like to take.. chance of low INR.
INTERVIEWER: umhm. OK. So ummm.. what are thee umm.. obstacles that you usually.. encounter.. err.. when.. doing the dosing.. and the INR monitoring er like in getting the INR into the range and maintaining it into the range do you have any.. obstacles or any difficulties in that?... and in what situations?
TAJ: ….. er… th' th' there are few patients.. adolescent patient.. with the.. mechanical valves.. who we sometimes question their dosing and they have er.. sort of.. um.. you know recreation thing or.. alcohol an' all these things.. so that sometimes.. er.. interfere with the… controlling of.. their INR.. within range.. and er.. few of them.. would.. even **miss**… er warfarin.. so we are not sure exactly.. whether it is.. true reflection of er.. you know.. INR changes… or is it.. something because of er… compliance issue.
INTERVIEWER: alright.
TAJ: err that we see. And.. in younger age group… because… again.. heart.. problem and.. they get frequent chest infection and these things… so.. that.. situation arises with… nearly.. every kid.. during the year when they get.. er.. you know infection.. then their INR definitely.. changes.. and sometimes we have to admit them to… control in either way with very high INR.. going above 6 or something.. and err.. with very low INR as well.
INTERVIEWER: OK. So yeah those things like er infections and err..
TAJ: infections compliance.. and obviously diet and these things...
INTERVIEWER: OK.
T : these affects err..
INTERVIEWER: umm so err.. let.. yeah.. umm just need to ask about compliance and and er patients when they do.. umm.. I've got some patients who do their own dosing.. or non.. non compliance regarding the interval of INR measurements so.. umm.. what is your **reaction**… with those patients.. usually?
TAJ: so we we try to e' err.. do frequent monitoring.. again.. because all of them.. are.. doing.. home monitoring..
TAJ: er and then calling us. So.. e' e' er.. there are only few patients which we have recognised who have very.. sort of.. variable reading.. er.. within 'is.. so those we do frequent monitoring..
INTERVIEWER: those who.. who make their own dosing so they.. they just do not follow the doctor's dose.

TAJ: e' e' the the.. most of the.. oh.. thi' this is very rare thing.. normally they follow what.. what you advise.
INTERVIEWER: yeah.
TAJ: yeah. It's er.. it's the missing the dose and sometimes.. for.. some reason..
TAJ: it's only I think.. **one**.. patient or.. I would say one or two.
INTERVIEWER: so yeah. What do you usually do in those circumstances when they do their own dosing?
TAJ: yeah umm….again.. er.. we can never know we only know is their.. INR.. once.. how fluctuates.. that is.. so if it still within range.. with.. bit of fluctuation or acceptable.. sort of fluctuation..
TAJ: um I mean accepting slightly higher INR.. in that situation.. so we still dose whatever reading we have..
INTERVIEWER: OK.
TAJ: accordingly.
TAJ: errr.. and that's thee…. er.. there are.. one or two as I said patients who.. who miss the dose for some reason and once we check and we find out.. we **have** found out that it is going low.. then we had to admit them.. to observe few days.. and that documents.. when they are admitted.. their INR.. behaves like er um um relatively.. stable sort of thing so their.. doc'.. that.. er tells us that.. probably there is compliance issue with.. with them.
INTERVIEWER: OK.
TAJ: because when you monitor them in hospital.. three days four days.. admitting them for.. other anticoagulation starting on heparin an' givin'.. so their INR in hospital… looks more stable..
TAJ: while…. time to time.. at home so.. there is complian'.. so this.. these are the measures.. so.. frequent monitoring.. and er if we have sort of..
INTERVIEWER: is there any specific like **formal** action with them?.. especially if you find that they they do they do their own dosing and the INRs are unstable?
TAJ: yeah.
INTERVIEWER: or out of range?
TAJ: yes when they are admitted there is some counselling sort of advice.. kind of things when we just suggest and that's talking to them.. errr… mostly they do understand and try to it is… but still it happens.
INTERVIEWER: OK. So in those few cases that.. they do their own doses do you find them.. **right** in their dosing or.. no.. usually.. those cases?
TAJ: because e' e' this is difficult to know.. this is only when they skip an INR goes low so obviously they are.. not taking probably..
INTERVIEWER: OK.
TAJ: regularly. But.. own dosing if we have an INR within range.. umm…. it's difficult to say whether they are doing their dosing because we have prescribed something and we are getting the INR.. exactly what… you would like to be.
TAJ: it's only when they don't take..
TAJ: normally they.. they follow.. whatever you are.. it's only **few**.. errr… mothers.. who sometimes.. ya that.. also.. one of the thing happens because sometimes.. umm…. we prescribe the dose.. just looking into.. one or two previous.. dosing pattern.. err.. an' in that case mothers they are.. probably more sensible they.. they ask us they discuss us.. they don't they suggest..

TAJ: OK probably doctor this dose is err.. I think this is.. a bit too much his INR will go very high because that has happen.. sometime I got that.. so we… with that discussion.. normally wee.. we come to an agreed dose..
INTERVIEWER: alright.
TAJ: it.. but um.. er.. even patients they.. they don't do their own dosing without being.. informing the doctor because.. on that side.. even they feel that.. the doc'.. the prescribed dose is **not**.. accurate..
TAJ: still they would like to discuss because they don't want.. take chances of.. prescribing themselves.
INTERVIEWER: OK.
TAJ: so that is.. e'.. err.. generally not happening or I… in my practice I don't see that.. patients are doing without.. doctor being aware of.. their own dosing. Because once they.. ask us.. they would like to discuss so we know the dosing sometimes we change… in.. you know with patient's experience.. and.. that is.. again if we feel that is sensible.. that is that is err.. umm that does work.. I mean that does happen that.. patients have suggested different dose.. and the doctor has agreed with that.
INTERVIEWER: alright.
TAJ: so.. that is occasionally.
INTERVIEWER: OK. Um so I just wanted to ask about thee err.. **stability**.. of INRs like you know.. keeping them in range.. umm.. we see that some pa'.. some people are quite… nice and they are.. let's say.. most of the time in range and some.. people are not.. and they are quite unstable.. umm so err.. are there any specific reasons behind that?
TAJ: …. err… again you never know.. err.. dietary pattern.. ummm.. which affects.. INR.
TAJ: errr….. e' it is true that there are a few patients whom would do see.. more fluctuation or I would say… they have um.. a greater response of little change in the dose.. so if you… increase dose slightly.. because of.. their.. low reading.. you find it.. going very high so they have a very **narrow** sort of dosing.. range.
INTERVIEWER: OK. So is there a specific reason behind that?
TAJ: ahhh.. I'm.. I'm.. I'm not sure exactly what is their… metabolism or kind of whatever.. liver function… err… how does that affect because there are few known factors…. interactions with drug and these things which you… but n'..
INTERVIEWER: yeah the known factors.. what are those **known** factors? (laugh)
TAJ: yeah I mean these are antibiotics and these things.. we know them.
INTERVIEWER: OK.
TAJ: errr vitamin K sort of th' situation if they are taking.. umm.. some some vegetables.. who are rich in vitamin K.. there are few.. so something like that but.. sometime.. not every time you know exactly why it is happening with some patients whether it is.. **own**.. coagulation.. cascade kind of thing.. which affects their.. individual INR.
INTERVIEWER: OK.
TAJ: but in practice I do see.. that there are patients who have a very.. narrow sort of er.. dosage range.
INTERVIEWER: yeah.
TAJ: that little change.. their INR changes..
INTERVIEWER: yeah well those like you know they have those.. um.. very fluctuating INR..

TAJ: yeah er but..
INTERVIEWER: is there any reason that you can maybe.. deal with.. to get them more stabilised? And what kind of patients are those with.. fluctuating INRs?
TAJ: errr.. it's only **few**.. it's very few it's not er… because if.. wee… percentage bu' I can not say.. percentage..
INTERVIEWER: yeah of course they are very few.
TAJ: but they are.. definitely very few patients.. errr.. they definitely need.. more frequent monitoring.. and err..
INTERVIEWER: do they have like a specific… **disease** like you know.. Fontan's versus valves? Or age maybe.. play that part.. so they have this labile INR?
TAJ: I.. I'm.. not sure.. I haven't er.. tried to explore this in.. in fact.
TAJ: er it is er.. exactly.
INTERVIEWER: from my own.. experience with people I can see that those with valves..
TAJ: umm.
INTERVIEWER: especially those with.. mechanical valves mechanical mitral valve..
TAJ: umm.
INTERVIEWER: er tend to bee.. **unstable**.. and they have very.. you know fluctuating INRs and.. as well as those who are very young..
TAJ: yeah.
INTERVIEWER: like you know one two.. or maybe below one year old.. so.. have you.. got umm..
TAJ: now that is.. that is true.. but e' e' on the other hand.. that is.. we are monitoring them more.. carefully or more.. closely so that's how.. we get all these fluctuations.. more.. recorded or more documented..
TAJ: mitral valve especially.. umm.. compared to Fontan because we have a big range we are.. much relax in prescribing Fontan patients because we know.. there is.. we can accept as low as 1.5 and we can accept as high as 4 or 5..
TAJ: so there is a big range of them.. we are not.. so.. and we are not monitoring that closely so.. that maybe one reason.
TAJ: we are not.. picking them.. or their fluctuation.
INTERVIEWER: OK.
TAJ: there there is more chance of fluctuation because they have a derange liver.. err Fontans.. because of the stasis and these things so we can ex'.. expect.. more fluctuation.. with someone who has derange liver function..
TAJ: which is Fontan group.. but we are not seeing much there because.. we are er.. monitoring them.. four weekly or.. **less** frequently.. so.. that maybe one reason..
INTERVIEWER: OK.
TAJ: that we are documenting more… if we are doing more monitoring… three days five days check in mitral valve so you will see more fluctuation.. if we m'.. errr.. you know.. monitor them in two weekly probably we would have… similar sort of err.. monitoring profile with them.
INTERVIEWER: alright so umm… er the other thing is the.. err.. the INR monitoring.. err so sometimes I see for some patients err when the INR is just out of range.. errmm.. the doctor.. like stays on the same dose and gives a long interval but for some others they do change the dose and give a shorter interval is there.. which was confusing for me so errr.. is there any reason for that?

TAJ: … you know mitral valve... especially mitral valve… and aortic valve.. or mechanical valve thing..
TAJ: there err… we do change the dose.. sometimes because we are doing very frequent monitoring.. and the range for them is er.. th'… the upper range probably we can extend and we can **accept**.. relatively higher range.. but thee.. you know.. below therapeutic we are not accepting so.. above 2 or 2.5 in.. most of the cases.
INTERVIEWER: OK.
TAJ: so that is.. one of the reasons there.. there many dose changes… and Fontan group.. although they are on.. there is.. e' e'.. because you are not worried of bleeding even… after 6 even.. if INR.. in.. you know.. practic'.. in practice I haven't seen.. patient.. who **bled**.. even with high INR.
TAJ: so you are not worried yes you want to maintain them somewhere between 1.5 to 4 but even 5 an' 6 an' 7.. we haven't seen many bleeding in practice.
INTERVIEWER: OK so you so you do concern about those.. with **low** INRs greater than those with..
TAJ: (at the same time) espe'
INTERVIEWER: (at the same time) high.
TAJ: yeah especially with the.. mechanical valve.
INTERVIEWER: OK.
TAJ: because there is.. element of clotting.
TAJ: in er.. err.. Fontan group even their INR is **low**.. we can still.. build up in.. next few days so we are not worried of.. you know.. if they have a transient.. few days.. of low INR.
TAJ: and that is the reason for.. checking them less frequently.. err and… upper range I'm not.. concerned most of the times because we first.. we seee.. we haven't seen any complication.
INTERVIEWER: bleeding one?
TAJ: bleeding.. yeah er I mean.. with the with the reading of 6 or 7.
TAJ: and rarely we have to **admit**.. even if it is.. err you know very high to give them vitamin K. so we haven't managed.. or we um didn't need to manage..
TAJ: with high INR group….. as frequently.. because err first there isn't any.. sort of.. bleeding and once you stop the dose you come down and then you just observe. So rarely we have to manage but low INR group because of the risk of clotting.. is much higher..
TAJ: there you have to admit..
INTERVIEWER: (at the same time) alright.
TAJ: (at the same time) and give heparin.
INTERVIEWER: yeah.
TAJ: errr and in Fontan group.. you are **relax**.. because you know higher.. won't give them bleeding.. most of the time.. because we are accepting range much lower than theeee e' where you have the risk of bleeding but say upper.. higher limit is 3 or 4.. but umm.. 6 7 8 even up to.. we have seen.. we don't do anything most of.. except for observing.
INTERVIEWER: OK.
TAJ: so there is **much** big room for them.. even they fluctuate.
INTERVIEWER: alright.
TAJ: and even they go lower.. 1.5 or low.. still.. er it's it's not much.. that risk of clotting because there isn't any mechanical valve.

INTERVIEWER: OK.
TAJ: so we can only get away with a.. you know.. four weekly monitoring in that group even… this dose prescribing can I jus'..
INTERVIEWER: yeah yeah.
TAJ: yeah even WATCH study dose prescribing.. I never have.. er problem with the.. with the.. as far I remember.. with.. Fontan group. Whatever **dose**.. **usually** it is.. quite acceptable and consistent.
TAJ: er.. maybe if I'm going to prescribe maybe I would prescribe the same or.. slightly.. so tha' I don't see big err.. mismatch.. in sort of er.. err.. you know.. computer pres' prescribing and my prescribing.. and.. even if there is little.. it is acceptable. But um with the mechanical valve.. where you ha'.. you are.. monitoring more closely so you see more fluctuation…. simply because you are monitoring them..
INTERVIEWER: (at the same time) yeah.
TAJ: (at the same time) on daily basis.
INTERVIEWER: (at the same time) yeah.
TAJ: and you have less range of you know acceptability… of er.. low INR.. err.. so that's how… there.. you're more… but this WATCH study dose again I see.. problem with that.. errrr.. with mechanical valves sometimes.
INTERVIEWER: yeah.
TAJ: sometimes.. and umm again because of.. worry of low INR.. I do change.. rarely.. but again it's not.. that frequent.. most of the time it is er.. acceptable but if I have to change anything it's only if I have some concern.. that is only in that group.. err mitral valve.
INTERVIEWER: (at the same time) with mitral valve.
TAJ: where you are really worried of low INR.
INTERVIEWER: yeah er so with theee hi' very high INRs when do you usually stop warfarin at which level of INRs?
TAJ: .. er it's er…. there is some guidelines.. or.. some prac' individual practices as well.
TAJ: if it is more than 6.. still you do not stop… you just umm.. decrease the dose or half the dose because if you.. completely stop.. and then the next day or the following day if it goes below their.. you know therapeutic that is more risky period.
INTERVIEWER: alright.
TAJ: if it is goes below… say 2.. that is more risk.. of clotting or.. clotting the valve.
INTERVIEWER: yeah.
TAJ: sooo you still you decrease the dose.. but you don't stop.. currently.. unless it is very very high if it is like 8 or sometimes we have from peripheral hospital refer admission with 8.
TAJ: you obviously admit them.. and suggest them close monitoring… but again on these valve group especially mitral valve group we **rarely**.. ask them to give.. you know.. vitamin K and these.. sort of things.
INTERVIEWER: yeah.
TAJ: again because of the risk because.. when you give.. and the INR goes low then (laugh) you end up.. givin' them heparin an'.. keepin' longer in the hospital.
INTERVIEWER: exactly. Umm OK so umm.. we can.. umm.. let's talk about like.. the new dosing.. model.. warfarin could you please.. errrmm reflect on your experience with.. with theee.. computer dosing?

TAJ: yeah er it is… I would say comparable or.. consistent.. with the.. dosing.. err.. slight variation… even there is some some.. you know.. interpersonal variation among the doctors… err.. the dose which I'm going to prescribe.. **not**.. necessarily exactly the same dose would be prescribed by my other colleague.
INTERVIEWER: alright.
TAJ: so there is some.. so.. within that sort of.. err.. acceptable variability I see the same.. dosing pattern in.. err.. computer because.. er…. I rarely have to **change**… or.. ask for change or.. have to call you.. and that rare situation is with mitral valve..
TAJ: but for err.. for Fontan.. and even for aortic valve.. normally it is consistent with.. whatever we have prescribing.. accepting.. some.. interpersonal variability as well.. err.. yeah so.. I think it is it is… within acceptable range of difference.. in dosing.
TAJ: the only thing where I'm very careful is um.. mitral valve.. but again.. **rarely** I have to change.. it's only **few** occasion when I have to call you or.. err.. so I feel it is.. e' e'.. I don' know how.. it is quite matching what we are.. prescribing.. it's close to that.. if not exactly…
INTERVIEWER: the same. So are there any advantages or disadvantages that.. um you have noticed with this process of dosing?
TAJ: … umm….. errr.. advantage in the sense um…. that er.. obviously there **maybe**.. more consistency.
TAJ: if it works… er.. or if it cont'… er.. if.. you know.. we have seen it.. more.. I'm not sure because if… we have a consistent dose.. if we have a sort of comparable dose or correct dose prescribing an' it continues.. so there is.. likelihood of more consistency.. or uniformity.. of the dosing pattern.. because… among the doctors.. we have different persons prescribing so that sort of.. variability won't be there.
TAJ: err if there.. and if weee.. could document sort of.. more er.. longer.. errm.. INR stability.
TAJ: … errr… then obviously.. that is that is.. err.. sort of advantage on the… yeah.. e' e' less confusion for the paren' maybe patients as well.
TAJ: err.. because of the.. umm… stable dosing.. or coming up with the computer an'.. yet maintaining the INR within range… errr… disadvantage being…. I haven't seen.. but you may **miss** sometime if we.. are trusting too much..
TAJ: you know what I mean because.. sometimes I do see I say OK.. an' I e' e' agree with that.. but if err.. you know.. sometimes you have to really question.. err.. that er… errr.. whether that umm… **is safe**… umm.. in terms of mitral valve.. like I have to.. do it f'.. err.. one or twice.. umm.. I felt that my dosing was.. obviously.. err.. correct.. in terms when we.. when we saw the response… so the.. disadvantage **maybe**.. potential disadvantage that if it is missed.. if it is overlooked.. the dose which has been prescribed..
INTERVIEWER: sorry what do you mean by missed?
TAJ: er I mean not cross checked.. sometimes.. if you are trusting too much.. because I don' know whether.. err.. a dose..
INTERVIEWER: so do you mean the doctor .. miss the checking.. the dose?
TAJ: yeah.. if the doctor..
INTERVIEWER: because we always.. there.. there should be always..
TAJ: (at the same time) yeah there is a cross check..
INTERVIEWER: (at the same time) a doctor that signs for this.

TAJ: yeah if trusting sometimes if it is like.. er.. trusting…… the dose what.. where has been prescribed by the computer.. because when.. you are prescribing you go through definitely in.. (laugh) every detail..
INTERVIEWER: (laugh) yeah.
TAJ: you see the INR you see the previous you see the pattern an' all these things because you are prescribing… errr.. an' if there is a dose prescribe and you are jus' signing.. sometimes you may.. not see the whole pattern.. so you.. you may miss the doctor who's cross checking..
INTERVIEWER: yeah.
TAJ: that maybe has.. so like but I'm not sure..
INTERVIEWER: so do you mean that umm.. thee err.. computer might not.. taking the clinical picture into account?
TAJ: … because I have.. since I have…. corrected in my.. sort of understanding once or twice..
TAJ: and.. err e'.. I wa'… e'.. I was not agreeing.. exactly the dose prescription by the computer..
TAJ: e' again.. very.. few occasions.. I would say two… two.. yeah two or three maybe.. err 'nt that many.. so if er on those two or three occasion… I may have.. I may agree with the er.. you know thee dose prescribed by the computer..
INTERVIEWER: OK.
TAJ: so I may jus… um.. you know.. the' that is something… err I'm not sure whether.. errr.. that was going to **impact** the patient… if we have.. checked the INR so that is something.. er.. if.. trusting… wholy.. on the.. WATCH… is.. it is premature… whether we can just do that.. so that I feel that umm… there isn't any harms (laugh) so far..
INTERVIEWER: yeah.. but.. yeah..
TAJ: but that I see as er.. as er… at the moment.. errr… that you have to re' be really go through… that whatever.. we have like cross checking thee.. computer dosing.
INTERVIEWER: ya this is this is thee ethical errmm… the ethical approval we haven't got that till we.. we have to assure that the doctor would.. should review the dose and check it and then.. prescribe it we can not do that.. without.. you know..
TAJ: umm.
INTERVIEWER: the doctor's agreement.. in any way..
TAJ: yeah.
INTERVIEWER: soo.. yeah.
TAJ: ya I mean if we are trusting that may.. sometimes it.. it may happen because those.. two or three occasions I am talking about… it maybe again.. I would have.. agreed.. there was a.. **chance**.. that I.. may have OK that's fine.. probably with the computer dosing rather than exactly.. questioning and these things.
INTERVIEWER: OK.
TAJ: so that is something.. er I would just like to say at this point.
INTERVIEWER: alright. so any other disadvantages.. with the computer dosing?
TAJ: …..mmm.. I don't see any major difference or any.. sort of er..... at this point.. to bring out as far..
TAJ: because… most of the time.. we… we are not.. errr… and… advantage an' another thing that.. you don't (laugh) have to.. wait for the doctor's time to.. calculate.. he has to just… agree.
INTERVIEWER: yeah.
TAJ: er… heee.. er.. doesn't need to think..

INTERVIEWER: (laugh).
TAJ: err.. (laugh) about going through.. er.
INTERVIEWER: so.. ummm.. err do you recommend this.. computer dosing to.. would you recommend that to other clinicians in the same area of congenital heart disease?
TAJ: …… um…. er.. I think it….. e' e'.. probably needs more time or more… to establish.. that it is yes.. it is.. convenient.
TAJ: in the sense that you… sometimes you can prescribe.. and there is very little sort of err.. discrepancy if there is any… those.. few occasions where I change the dose.. again.. that may happen with my other colleague.. he may have.. have agreed.. so computer dosing I feel is um.. err…… quite appropriate um.. I think it is.. but it is.. difficult to say whether err..
INTERVIEWER: to be applied like in the usual..
TAJ: (at the same time) to be applied completely.. ye'..
INTERVIEWER: (at the same time) usual clinical care?
TAJ: e' in in practice.. but um… again it seem whatever.. I think e' it is.. very forward.. **it can be**.. a replacement.. without.. because if doctor is not.. the point where.. I think we should be aiming at that.. there isn't any need for doctor… still we are cross checking so there hasn't been any independent prescribing but er.. so if that is the case.. still I think it is it is um.. probably very forward… because.. mm we have only few occasions.. where we need to change the dose so that means it is er.. in vast majority it is quite applicable.. and umm.. err.. it's fine and even.. if.. we take it that few occasion where I have to change the dose.. if would.. would happen with.. with other colleague or with.. you know.. sometimes..
INTERVIEWER: yeah of course.
TAJ: you have.. so you do see.. um um.. sort of fluctuation in INR anyway.. in normal prescribing..
INTERVIEWER: yeah.
TAJ: so if computer is.. prescribing and then you see that fluctuation… that is again.. we we can increase sort of margin of safety accepting slightly higher dose or higher range.. for those valve group..
TAJ: where.. we can.. we know there isn't.. there is not much risk of high INR.. or there is greater risk of low INR so if you put a higher.. range.. then you have an.. computer dose pre' prescribing would be even more safe.… because you.. are then not going low.
INTERVIEWER: alright yeah.
TAJ: so that err.. in that ca'.. in few cases where you can just.. give a more safety margin.. and then you can accept this computer prescribing.. in practice sort of.. errr as a way forward.
INTERVIEWER: alright. So like um do you prefer it like to.. um.. to replace the doctor dosing.. totally or like to be in combination like a computer dose plus… doctor's..
TAJ: yeah..
INTERVIEWER: judgment?
TAJ: yeah until we all (laugh) until we have.. er.. as I said it looks quite acceptable.. it looks umm comparable… with err few exceptions which is again which can happen in normal practice.. soo.. it can replace.. it can replace doctor prescribing.. because it's um.. errr… there isn't err.. a sort of.. risk of harm..
TAJ: or there is very minimal risk of harm if we jus'… address with few sort of err situations where we can avoid that.. I think computer.. can computer dose pres'

prescribing can be.. a good practice.. err or as an alternative…. umm.. to doctor's err prescription.
INTERVIEWER: yeah.
TAJ: prescribing.
INTERVIEWER: so umm any other recommendations? Umm regarding this computer dosing?
TAJ: ….. umm…… mm…… I think that er….. I'm not sure whether we have any data of… errr.. you know this monitoring thing.. the space… space thee you know this um… checking of.. umm this.. INR monitoring thing.. we can.. as a firs' step.. we can do.. less frequent monitoring for.. especially for those cases.. errr who have stable INR or these things… e' prescribe by the computer I don' know how.. you determine that monitoring.. so if we..
INTERVIEWER: so' sorry do you mean the interval.. of the..
TAJ: (at the same time) interval of..
INTERVIEWER: (at the same time) INR monitoring?
TAJ: yes.. interval of..
INTERVIEWER: it doesn't give the.. the interval of monitoring it's it depends on my judgment so and it depends on how stable is the patient.
TAJ: so who who is er picking up all case.. do in three days or two days.. or one week or two week?
INTERVIEWER: er it's me.
TAJ: yeah.
INTERVIEWER: yeah.
TAJ: so if we.. change that or we.. increase that sort of err umm interval..
INTERVIEWER: increase the interval?
TAJ: interval.. and see the stability.. because more frequent you err check more frequent you do the changes.
INTERVIEWER: yeah.
TAJ: accepting a **bigger** range…. and.. er.. e'.. differing or changing the interval..
TAJ: to err sort of err.. e'.. longer period..
INTERVIEWER: yeah.
TAJ: … err to start with.. and that probably.. an' then.. in few months we may.. er..
INTERVIEWER: yeah.
TAJ: feel that it maybe..
INTERVIEWER: we've got yeah this problem because umm umm.. the.. practice is different from you know.. from research um because it's a research so when the INR is just out of the range I have to do like.. monitoring more frequent.. because.. I have to be stringent with my target range but in practice it's.. different so you may go for…
TAJ: yeah.
INTERVIEWER: a longer.. you know longer interval and just.. **accept** that dose.. but because of.. research purposes so.. we are doing a study so we need to know.. **how**.. efficient is the computer in adjusting the dose.. so that's why we are umm… dosing more frequently.. in some cases.
TAJ: yeah.
INTERVIEWER: but again if it is stable and it is within range for some people so we do like a wider range.
TAJ: yeah if we incre' if we widen the range.. probably that would help.. in reducing you know.. checking the.. monitoring thing.. and that would also relax.. because e' in

practice I do see.. bigger range.. even they're fluctuating.. we put a target range… two to three two to four.. and then.. we see it is going to 4.4 or 4.5 or.. it is till acceptable.
TAJ: ya you can bring it **down**..
INTERVIEWER: yeah.
TAJ: but it is still acceptable… er.. but in few cases especially in.. valve cases you don't want it to go… lower than certain.. so if we put.. sort of higher range.. from 2 to 5.. 2 to 4.5..
TAJ: because we know we.. I have not seen a single bleeding with 5.
INTERVIEWER: OK.
TAJ: few exceptional cases you have to do individual monitoring..
INTERVIEWER: (at the same time) so it all depends on..
TAJ: (at the same time) you can.. leave them..
INTERVIEWER: (at the same time) practice.
TAJ: (at the same time) yeah so if we increase the range.. bigger range.. wider range.. that would.. relax the dosing even.. we know we are.. and we just.. **up** the lower… limit.
TAJ: OK it has to be above say.. 2.5.
INTERVIEWER: OK.. the lower limit is going up.
TAJ: yeah so we know.. there is a safety margin added.. that even if it goes below.. lower than that or.. fluctuates within.. that narrow INR.. still it would be.. not very low.. and then.. upper limit we increase extend it too.. yeah.. so that would er.. and then we do less frequent monitoring..
INTERVIEWER: yeah.
TAJ: maybe that would…. umm.. that would er relax the dosing sort of thing… I think still we do.. frequent monitoring.. I would like to say that.. even for valves.. it should be more than two weeks…. ideally I would la'..
INTERVIEWER: er is it like the.. is that the doctor's.. prescribing.. or the computer's prescribing?
TAJ: … e' it's the practice here I would say.. it's just the practice.
INTERVIEWER: so you would like to make it longer?
TAJ: yeah.. ideally two weeks minimum.. er er for the for the valve thing.. e' in in obviously in Fontan group three weeks four weeks monitoring is.. reasonable.
INTERVIEWER: alright.. alright. Do you have umm any other comments that you would like to add?
TAJ: .. I think I have (laugh) said what I.. err had to say.. that's err .. these are the only things.
TAJ: thank you for giving this opportunity.

## C- Nurses' interviews

### 1- Interview number 5: HCP3

INTERVIEWER: umm.. hello..
Shirley: Hi.
INTERVIEWER: and thank you so much for agreeing to take part in my research.. err.. the purpose of our meeting is to talk your.. experience with warfarin dosing and.. monitoring before and.. after using the new warfarin dosing model.. err.. so first I would like to set the new warfarin dosing model aside and.. I would like that.. umm.. you let me know.. err.. about.. the general approach that is being used for warfarin.. dosing and monitoring and your.. **role** in this process.

Shirley: OK.. umm… I think the way that families have been recruited has been really.. really good.. umm.. I think there's probably… family who.. 'a migh' be.. probably wouldn't 've recruited.. umm.. who.. e e.. you know.. had maybe not been too compliant beforehand.. umm.. so I think them so' of joinin' the study…. I probably would 've said.. **no**.. bu' I think the process for the other families has been **fine**.. I think it's been a good **mixture** of families **as well**.. umm..
INTERVIEWER: err.. excu'.. sorry..
Shirley: it's OK.
INTERVIEWER: err.. I just need to.. to know the.. **approach**.. the usual **approach** used in warfarin dosing and monitoring before.. err..
Shirley: err.. sorry..
INTERVIEWER: the trial.
Shirley: OK..
INTERVIEWER: it's alright (laugh).
Shirley: so beforehand.. umm.. obviously if if patients who are going to start on warfarin.. umm.. we would see them in the.. pre-operative clinic..
Shirley: umm.. give them some.. written information about.. warfarin.. umm.. effects of it.. umm.. and go through all that information with them.. and then when the patient came to the ward.. um.. after surgery.. umm.. we would again if.. go through tha' information with them.. umm.. so if they've go' any questions.. and then.. if the family were wishin' to do home monitorin'.. umm.. then we would go through the trainin' package for doing home monitoring for them. Some families don't wish.. to do tha.'.. umm.. for various reasons.. umm… some families jus' don' want to be.. pricking the child's finger..
Shirley: umm.. jus' say no they'd rather.. you know.. we.. we did it.. umm.. some families have gone to the local hospitals although that's sometimes qui' difficult to try to organise that 'cause a lo' of centres will only see.. adults not children.. umm.. or they'll have set times for the GP surgery or the.. hospital.. which again is a down side for families because.. they 've had pos' take time off work or time off school to actually go.. to those appointments..
Shirley: umm…. So that's th'.. the way that we see the families **all** families who.. err.. all children who are gonna start warfarin would see all those families and hopefully we've met them 'n give them the information beforehand..
Shirley: umm.. weee….as a… as East Midlands **team**.. we.. prescribe for all of our families.. so I know in some centres the.. umm.. children refer refer back locally.. umm.. to the local hospital and they would do the dosing bu' where if e' families are within the East Midlands.. umm.. our doctors here would still continue to do the.. the dosing..
Shirley: whether they would being home monitored or they were.. umm.. bein' tested elsewhere..
Shirley: umm… we do have a couple of families who.. do actually get dosed by the local hospitals as well but the majority.. umm.. stay.. stay with us.. and stay with us untill they're 18..umm.. and then transfer of it to adults services which is another issue.. (laugh)
Shirley: umm.. so.. umm…. So if the families who who are gonna do the home monitoring.. we would do.. the training package which would normally be probably sort of 3 training sessions with them..
Shirley: we have a contract.. umm.. that families need to sign to say that they will.. umm.. do the testin'.. umm.. to say that they will bring the machine to back in for

comparison check against our machines.. the GP has to be in agreement.. umm.. that they will prescribe strips for them..
Shirley: so the machines get bought for us by charity.. umm.. but the strips have to be prescribed by the GP..
Shirley: we did have an issue with that a number of years ago when tha' lots of GPs would say they wouldn't prescribe them.. because.. umm.. they're already provided in anticoagulation service the GP practice..
Shirley: and therefore.. they were prepared to then be payin' up for prescriptions.. for wha' they source of separate service..
Shirley: that changed and.. umm.. certainly there was a new agreement with the **Leicestershire** GPs.. that they would all sign up to.. to children havin' the.. the warfarin strips.. and I think that.. umm… that 'ad sort o' come from the government.. umm… but it'll als'.. sorry from the company.. umm… but it'll also from sort of charity isn' that as well.. umm.. so that they change so we don' have the promise that we used to have with.. umm… GPs saying… though we won't do the testing…
Shirley: which for some families was.. was… you know.. a nightmare really trying to get here..
INTERVIEWER: so in your experience.. errr… with the families.. errr.. do you usually see that it's easier for them to check at home or it's.. easier for them to.. go.. or to check locally?
Shirley: I think it's easier for them to check a' home because they can.. they can do it before school after school before work after work..
Shirley: so that they're not takin' time off work or school.. they.. barin' in mind that families 've.. had a huge amount of time off work or school to be in hospital anyway..
Shirley: umm… I think if the children are poorly or they 've started medication then obviously we'd say to check sooner.. which again.. if that's the weekend.. that's a problem if.. if they're goin' locally 'cause clinics are usually jus' Monday to Friday..
Shirley: umm.. if they're goin' on holiday.. they can take the machine with them.. bein' in this country or.. or abroad.. umm.. so I think the machines make made **a huge** difference..
INTERVIEWER: alright.
Shirley: I think certainly when I firs'… started in this role.. all the families had to go to the local hospital.. or they used to have to travel here for it doin' so some families will travel two hours.. for a blood test n' then get back home again..
INTERVIEWER: oh.
Shirley: so completely **changed** people's lives.
INTERVIEWER: great.. so.. umm.. now we go to the.. er.. process of warfarin dosing and.. monitoring.. errr.. when does.. err.. when do doctors usually start.. warfarin.. for patients?
Shirley: so it depends how they've come to us so if it's a patient who maybe a Kawasaki patient.. you wouldn't.. be..
INTERVIEWER: sorry?
Shirley: the patient with Kawasaki's.. disease..
INTERVIEWER: umhm.
Shirley: wouldn't.. they would come in as a.. as an emergency admission so that wouldn't be.. somethin' that you've planned for in advance.. umm.. so they would.. start that when the'.. they are admitted.. umm.. for children where it's a planned.. umm.. have

a valve replacement or for Fontan's circulation.. umm.. they would be on heparin and then they would.. umm.. start the warfarin as soon as they were toleratin'..
Shirley: the.. oral feeds.. umm.. so usually a few days post.. post-surgery.. 'n then they'd have an overlap between warfarin and.. the heparin.. umm.. until they get the levels.. levels up.
INTERVIEWER: alright. And.. umm.. err.. how about the.. errr.. INR monitoring and dose change changes how often.. err.. are they usually made?
Shirley: ...
INTERVIEWER: at the beginning and then..
Shirley: at the beginnin' it's if.. it's usually daily.. that they're tested.. umm.. and then it changes to.. either of a few days or a week until they're nice an' stable.. umm.. they ten' not to go more than a week.. when they're… when they're first.. started..
Shirley: umm… and probably a lit'.. a little bit more cautious.. well certainly are a bi'.. are more cautious with the.. valve patients than they are the.. say the Fontan circulation.
INTERVIEWER: umhm. So.. umm.. what's the reason behind that? Being more cautious with valve patients?
Shirley: some centres don't actually give.. warfarin for Fontan patients.. umm.. but obviously we.. we do here.. ummm.. so their range is lower.. umm.. and.. if their levels are lower then it's not as a disastrous the fact as it would be if you got aee.. mitral valve in place 'n their INR is low.. umm.. which obviously could be.. be disastrous 'n the valve could block off so.. umm.. so that's why they're more.. more cautious with them.
INTERVIEWER: aha. So.. errr.. and.. umm.. what are the **obstacles** that.. err.. do you usually encounter in getting the INR into the target range and in maintaining it.. in the target range?
Shirley: I… th..ink that.. sometimes it's when your doctor start.. umm.. I think if you go' a new.. wa'.. here.. we only have our cardiology registrars 'n i' only the registrar who can prescribe...umm.. so the paediatric registrars can't.. umm.. so again it depends how much experience they 've had of prescribin' warfarin.. umm.. and they're sometimes probably a little bit more.. **cautious**.. umm would maybe say.. check more sooner than…some of the.. more senior doctors..
Shirley: umm… umm…..I think some tryin' to ge'.. sometimes tryin' to ge' hold of the doctors to actually.. prescribe them.. other tha' is gettin' better.. now we all share an office together we go' easier access to them we used to spend huge amount of time to.. chasin' them.. umm…. I think the families ringing in.. umm.. I think initially families are very good at ringin' in.. and… when you say to families well.. you know.. some families do not ring for a month or 6 weeks 'n they meant to 'n they've always **shocked** by tha'.. 'n then the other ones who.. you know.. you're ringin' them sayin' you've not checked the dose.. umm.. others are **absolutely** on the day they'll.. they'll phone through.. err.. very meticulously.. umm…… I think they are the main problems to.. jus' repeat the question again.. I missed a bit..
INTERVIEWER: umm.. (laugh)
Shirley: (laugh) sorry.
INTERVIEWER: yeah.. the obstacles in maintaining.. getting the INR into the target range and in.. err.. maintaining it..
Shirley: yeah.
INTERVIEWER: in the range.
Shirley: I think sometimes people…. 'n again if they don't know the child sometimes will make changes in the doses.. when.. if you actually **look** back over.. the child's

prescription chart you see they do fluctuate slightly but actually if you leave them.. so certainly some of the teenage girls.. 'n I know that the haematologist will say.. the menstruation makes no…. **difference** to it.. a lot of our girls will say their INR is very different when they're menstruatin'.. 'n actually if you jus' look at tha' pattern bu' you leave them on the same **dose**.. they will return back to normal.. umm.. but I think people who maybe aren't as.. familiar with them will change the dose.. 'n then you spen' weeks tryin' to… ge' back to where you.. you were to get back into range..
INTERVIEWER: umhm.
Shirley: umm.. 'n again it tha' seems sometimes jus'.. tweakin' little doses or….. do' not realisin' that actually the.. it'll take a couple of days to you actually see that effect so givin' the medication checkin' the next day.. umm.. 'n then makin' an'.. another change.. before allowin' that to sort of coming.. I think tha'.. you end up then sort of chasin' your tail.. to try to get back in range.
INTERVIEWER: so are there like.. err types of.. patients.. or indications I don't know certain conditions.. err… that.. err.. might affect.. the INR stability?
Shirley:…. So again if a child go' an infection.. umm.. or startin' antibiotics.. umm.. we do find when children go on holiday.. if they're eatin' different.. things as well on holiday or.. drinking.. so the.. teenagers who might be having the.. a drink.. umm.. so they'll have an effect on it as well..
Shirley: umm.. sometimes people do mit.. miss a dose.. 'n I have 'o say mos' of our parents are very honest 'n 'll say.. completely forgot to givin' the dose at the weekend so.. again we'd rather know that.. when you… when you're dosin' to know that they've missed the dose rather than.. you know.. altering' a dose thinkin' you're not givin' the correct one..
Shirley: umm.. I think some of the teenagers when the parents are tryin' to get them to.. umm… to s'.. to start takin' control of their own medication.. they will often forge' er.. forget the dose.. but again.. they tend to be fairly honest 'n say.. I forgo' to take it..
INTERVIEWER: (laugh).
Shirley: ummm…so… that the main thing I think.. yeah.. holidays.. food diet..
Shirley: changes in diet.. **babies' weaning**.. umm.. 'n we haven' got many youn' babies on.. warfarin I think we probably only go' one….. I can say under one bu' actually he's over one now.. umm.. but certainly.. know tha' er as a **baby**.. he was very difficult to tryin'.. manage his levels.. umm..
Shirley: obviously as he was growin' 'n 'en he started his weaning diet 'n.. umm.. 'n he was changin' formula feeds as well which.. umm…
Shirley: obviously the content of the formula feeds 'n they've got vitamin K in….
so…umm.. it's jus' those sorts of things will change it.
INTERVIEWER: alright.. and.. yeah how about.. errr… now the process of… errr… the.. process of.. ringing in the INR and then that process of.. prescribing and.. er.. getting back to patients the compliance of both patients and the.. all this process..
Shirley: um.
INTERVIEWER: ummm… do you usually encounter any difficulties in that?
Shirley: .. hh… I think sometimes it's volume of **calls**.. we get.. (laugh)..
INTERVIEWER: (laugh).
Shirley: I think that certainly increased.. umm.. you know when I think.. when we first started.. umm.. e' e'.. with the home monitorin' I think there was 3 patients on home monitorin'..

Shirley: umm.. ‘n then number of calls we get now so like some days we can have maybe 25 calls in a day.. umm… which barin’ in mind that’s.. part of our extended part of our role it consumes a huge amount of time.. umm.. I think tha’ probably there is a **need** for an **anticoagulation**.. service.. umm… I think..ye’.. you know.. if you takin’ the.. amount of trainin’ that’s havin’ with families ‘n callin’ them back to recheck the machines.. err.. takes a huge amounts of time so.. it is time consumin’ umm.. I think families **get to** know us though.. when we are phonin’ them ‘n I I think they like.. tha’.. that is a regular person contactin’ them.. I think.. families are… we’ve certainly got some families who are very good ‘n ‘ll say.. this is what their INR is today this is what they‘ve been havin’ this is what I think they should have.. ‘n ‘en the doctors ‘n ‘ll say.. umm yeah that’s yes I agree with that..
Shirley: so.. ‘n they usually correct..
INTERVIEWER: aaa..
Shirley: umm..
INTERVIEWER: the families are usually correct?
Shirley: they are.. they are.. yeah..
INTERVIEWER: sorry to focus on that point.. why do you usually.. err.. why.. do you think that they are correct? in deciding the dose?
Shirley: I think because they’re **looking** at… they know the child the best they.. they…. I think look a’ wha’ pattern there’s been I suppose to maybe jus’ lookin’ at the last couple o’ doses..
Shirley: I think they look back ‘n say.. well you know… we dropped before.. this is wha’ happened.. de de de.. be stayed on this dose.. ’n ‘n we went back to it.. so.. I don’t know I think they just… seem to know better..
INTERVIEWER: (laugh).
Shirley: ‘n I think… I think parents probably don’.. **change** the doses as much **as**.. the doctors would do..
Shirley: I think parents are often… are happier to say well actually.. it’s dropped **before**.. umm.. we left it at this.. ‘n i’ jus’ went back.. umm.. whereas I think we’re probably a little bit more cautious ‘n think OK we will change i’.. umm.. but then often it’ll be out of range though.
INTERVIEWER: aha. So.. so.. err.. who do you think is the best judge is it the parent or the doctor?
Shirley: …. Have to say for the parents who actually.. leave the doses the parents are normally right.. (laugh).
INTERVIEWER: (laugh).
Shirley: for the fear tha’ we have.. who say what they would.. I think they are.. usually right.. I think umm…. I think there are exceptions.. umm… to it.. umm.. ‘n some..
INTERVIEWER: do you have many of those families that do.. their own dosing?
Shirley: hhh… there are a couple of teenage.. umm.. ones ‘n some younger ones where the.. families are doin’ it.. umm.. what we’ve said is that we.. that the consultant has to say.. that they are agreein’ to it.. umm.. because again.. part of the agreement when they sign the contract it said they’ll phone in ‘n we do the dosin’.. umm.. so in those situations when families ‘ve said well I.. I don’t want you to do the prescribin’ because I think… mine is correct..
Shirley: we’ve said that the consultants must write ‘n say that they agree to the family.. doing it ‘n that is then not our responsibility or the registrars’ responsibility..
INTERVIEWER: so it’s the responsibility of the family?

Shirley: the family and the consultant who's agreed i'.. umm.. so.. yeah.
INTERVIEWER: and how about the others who are on who follow the doctor dosing are.. how.. how is their INRs?.. stability?
Shirley:… I think it's a mixture I think there 'r some.. some children 'r absolutely beautifully.. stable..
Shirley: umm.. you know 'n they're bein' tested every.. you know say the Fontans they're bein' tested every month.. 'n they 've been on the same dose for ages maybe till they 've a growth spurt 'n then they we need to increase them so I think there is some patients who were.. beautifully stable.. I think they are all the patients who.. nothing changes the diet doesn't change they 've not 'ad a growth spurt.. and they.. just.. are not stable 'n we.. we don't know why..
Shirley: ummm… you know I can think of a teenager patient who 've had who.. her dose goes up 'n down all the time she's adamant that she takes it when she's..
INTERVIEWER: sorry?
Shirley: she's adamant that she.. takes the dose.. umm.. bu' her levels were dropped really **low**.. 'n then the next thing they really **high**..Shirley: umm… one of th' things we looked at a one stage was she had actually **changed** her tablets of.. rather 'an havin' just.. one milligram tablet.. she'd gone to havin' some 5 milligram tablets as well..
Shirley: umm.. 'n there was a change in her actual.. umm… warfarin level her INR then.. umm.. so we didn' know whether there was…. e'.. we.. we didn' think it should 've made a difference 'cause she was still actually getting' the same amount of milligrams.. umm… bu' i'.. the.. change seem to coincide with the change in the actual tablets.. so.. we couldn' prove tha' bu' i'.. you know..
Shirley: they coincide.. ummm…. bu' 'n I don' know why some patients just are….beautifully stable.. 'n others.. er.. are no'.
INTERVIEWER: dose it have a relation with their… errr…errr.. indication of why they are taking warfarin?
Shirley: …. I would say the Fontan patients are probably more….**stable**.. but I think that's maybe because they are not tested as **frequently**..
Shirley: whereas the valve patients are tested more frequently 'n I think sometimes there is more.. room there for… changes in the dose… which then affects.. the range.. so.. ummm…. yeah.. yeah.
INTERVIEWER: in your experience is there any specific reason of why those patients with valves have this fluctuating INRs? And unstable.. INR.. control?
Shirley: I can' think of a reason.. no.. we jus'.. they jus' seem to.. 'n whether **it is** the.. the.. they're testin'.. more regularly 'n therefore the doses changin'.. bu' in some patients it's changin' more regularly..
Shirley: umm…because I believe in adults.. they don't test as frequently.. umm..
INTERVIEWER: er adults with valves?
Shirley: adults with valves.. yeah.. ummm.. 'n whether they are more stable or no' I don' know.. ummm.. but I know tha'.. w'.. s'.. certainly for children we'd say to test more frequently than the adults do..
Shirley: umm.. so.. whether this is a good thing or a bad thing I don' know if they're.. if they are stable.
Shirley: ummm… you know bu' i' get.. if you get a result.. you've obviously got to react to tha'.. the result that you get.. ummm… but.. um.. I guess it goes on.. in between those.. two measurements you've got you don't know you know it could adopted to lot

lower in between.. ummm… so.. I don' know why in some it is.. isn'.. isn'… don't know.
INTERVIEWER: alright. Umm.. OK. So.. er.. now.. I would like to.. talk a bit about the new warfarin dosing model so could you please let me know about.. errr… er.. your experience so far with this.. new dosing model?
Shirley: OK. Umm….. I **th**ink.. from wha' I can **see**.. is the… the computer dosin' for patients who are on warfarin… I think they are nice 'n stable.. 'n I think they.. they are.. I think it's workin' really well.. I think for the valve patients… for some patients again it's working really well.. for others.. umm… I don't think it is 'n I know there is a few occasions when we've.. overridden.. the computer dosin'.. umm.. you know if 'e levels 've been low.. ummm… then.. the computer is jus' at all give another dose.. whereas actually.. we would 've maybe givin' some.. some dalteparin or givin' a bigger dose..
Shirley: umm.. so know i' has been overridden.. umm… so.. 'n I think…. for most families it's been.. they've been fine it's been fairly stable I think there are.. a couple who've.. (laugh) done their own thing..
INTERVIEWER: (laugh).
Shirley: which obviously doesn' help the study..
Shirley: umm…. there are a few families who've questioned when we've said well the computer doses 'n..'n.. again 've said well actually we'd been on this dose for a certain amount of time why 'as the computer changed it..
Shirley: umm... bu' when we've explained to 'em well it's.. it's part of the study and you know.. it may be different what we would 've given…but actually.. that is part of the process that's what we are trying to compare families have been fine with tha'.. umm.. certainly if they 've no' been then we've come back 'n.. that you talk to the doctors 'n said.. there is families 've said they're not happy with this dose they already is gonna go one way or the other.. umm.. bu' I think most of 'em.. 've sort of accepted tha'.. that's what the computer said so we jus'.. they'd go with it..
INTERVIEWER: so.. ummm.. are there any.. errr… or errr… could you please let me know about advantages and disadvantages of this.. er.. er.. dosing model?
Shirley: ..hh..umm.. I think for **some** patients.. 'i.. it's… **been dosin'** more frequently.. umm.. 'n certainly there is a.. tha'.. the little one I was talkin' about his.. his dosin' on the computer system initially was.. umm.. he was been tested everyday.. umm… whereas.. I think if the doctors done i' we wouldn't have done it everyday..
Shirley: umm.. 'n think our concern form tha' point of view was.. umm… his mum said he's not bothered about i' 'n it doesn' bother him but I think we w'.. we were on long term the effects of having it… been for you.. dosed up everyday.. umm.. so I think tha' was one worry was sort of highlighted tha' was very frequent tha' was bein' tested..
Shirley: umm.. bu' equally.. his does.. his.. his INR does.. fluctuate a lot as well.. 'n whether that's because of his age 'n obviously they've been changin' diet because of he.. he's weanin' 'n he's growin' I don't know.. umm……. I think that's the main.. the main thing really.. I think this.. this..
INTERVIEWER: the main disadvantage.
Shirley: ..yeah I think that's it that was disadvantage was the more.. more frequent.. well then tha' probably is balances out with.. some of the other doctors who.. you know.. so he probably fairly even I guess tha'.. tha' particular patient jus' brings to mind..
Shirley: umm.. because it was frequent 'n we were.. we were concerned about i'.. umm..
INTERVIEWER: so it was for that one particular patient..

Shirley: yeah..
INTERVIEWER: what about.. for.. the others?
Shirley: to the others it's.. again it's sometimes more frequent than we probably would 've done certainly for the Fontan patients who.. maybe would 've 'n normally done every month.. umm sometimes they've been more frequent..
Shirley: umm.. then for other patients it's been.. umm.. you know they've been given longer than perhaps the doctors would 've given so..
Shirley: ummm…. but I think for the.. I think the ones who've been stable.. umm tend to be the Fontan patients more than the valve patients..
INTERVIEWER: again Fontans are more.. (laugh)
Shirley: yeah.
INTERVIEWER: more stable than the valve.. (laugh).
Shirley: yeah.
INTERVIEWER: OK.. err..so.. umm… err.. do you recommend this dosing.. err.. model for other clinicians in the same.. area?.. the congenital cardiac.. patients?
Shirley: yeah….. I think for s'.. for some patients I think it has worked... I think for others… I don' know the.. the research may show differently maybe jus' be my experience from looking at the charts.. umm… I guess we have to look at the.. the valve patients to see whether…. to do tha' proper comparison 'n 'en to see.. to see who's more.. I do'.. I don' think there is…. the computer system has not…. I don' believe pu' anybody **in danger**..
Shirley: umm.. by doin' i' I think there are.. obviously a few occasions where we've.. we've questioned that it's not said give dalteparin or give a higher dose.. umm... but I think… you would always have that fail safe... anyway..
Shirley: ummm…. don' know I think it seems to 've worked.. worked well… yeah.
INTERVIEWER: OK. So.. umm..do you have any recommendations to... for this model to make it work better?
Shirley: ….. umm…….. I can' think of any (laugh)
INTERVIEWER: laugh
Shirley: laugh. I can' think of any no.. er apart from maybe having a designated anticoagulation service would be lovely..
INTERVIEWER: laugh.
Shirley: 'n then having tha'.. havin' tha' model with… you know with tha' because think.. I think it's been… hugely time consuming..
Shirley: umm.. 'n think certainly when I.. I agreed to (nurse).. umm.. doin' the project I didn' realise it would be.. quite as time consuming as it.. as it was.. umm... but actually if the end result is going to be good and it's move the service forward or actually shows that.. you know yes we do need a dedicated service.. I think that's really positive.. I think maybe jus' because of our staffing.. levels at the moment..
Shirley: umm.. it's.. it's obviously had an impact on us.. umm.. but I think if the long term.. I.. you know..
INTERVIEWER: (at the same time) so at the moment does it have a..
Shirley: (at the same time) it's going to improve the care..
INTERVIEWER: yeah.
Shirley: 'n.. er.. you know 'n 'n a better service for families.. then that'll be.. be good.
INTERVIEWER: so at the moment does it have like.. er.. a negative impact on your service? Or a positive.. does it have like.. err.. putting mo'.. more pressure on you?

Shirley: …I don' think it's puttin' more pressure on us I thi'.. I think tha'.. tha' sort of.. e'.. the initial work that (nurse) was doin' I think it did.. I think the day to day basis doesn't unless.. families are not phonin' in when they should 'n it's in the evening 'n obviously we having to then contact you in the evening.. umm.. or.. but I think most of the time it's.. you know.. either you aren't around or umm.. you know to return the call so it's not as if we're waitin'.. for calls comin' through.. so I think on a day to day basis it's not…. not changed it really..
Shirley: 'n obviously if you are not around you've always told us.. you know you're not gonna be around bu' I'll be back later on so.. umm.. no I think the dosin' it's always done in a timely.. timely manner that's.. that's not changed so..hh..
Shirley: hopefully it'll.. it'll… improve i' (laugh).
INTERVIEWER: hopefully.
Shirley: hopefully.
INTERVIEWER: alright. So do you have any other comments that you like to add?
Shirley: umm..
INTERVIEWER: any other issue that.. umm… you.. may.. highlight you would like to highlight?
Shirley:… no I don't know how much information was.. given to.. sort of the nursin' staff on the ward 'n tha'.. before it started I don'.. I don't know.. umm.. because you know some of the.. the times we found is that the.. the families have phoned in over the weekend.. is that.. the staff 've got the.. doctors to.. prescribe it.. umm.. 'n then realised afterwards that.. although I've done that sometimes as well.. umm.. bu' then.. umm.. so it's only then when we picked it up after the weekend we realise actually the doctors have prescribed it rather than the computer..
Shirley: umm… so umm… I'm not sure how much.. they were aware or whether it's jus' because they're busy it's jus' consumedly do the INRs..
INTERVIEWER: yeah.
Shirley: because again the doctors were aware so the doctors who are prescribin'.. should see on the system I think the system worked quite well with the stickers on the folders that is clear.. umm.. who's supposed to be doing it so.. bu' I think that's probably.. maybe skewed some of your figures.. (laugh)
INTERVIEWER: yeah.
Shirley: a bit so..
INTERVIEWER: we've got those incidents.
Shirley: yeah.. yeah.. umm…… no can't.. can't think of anything else.. no.

**2- Interview number 6: HCP4**

INTERVIEWER: umm.. hello.
MADISON: hello.
INTERVIEWER: and thank you so much for agreeing to take part in my research.. err.. the purpose of our meeting is to talk about.. your experience with warfarin dosing and monitoring.. err.. before and after using the new warfarin dosing.. model.. umm.. so.. err… at first please let's set.. the warfarin dosing model apart.. could you please let me know about the overall approach.. er.. that is being used in warfarin dosing and monitoring?
MADISON: err.. yes it's OK….. for me this is.. this interview is really simple.. right? … when it comes to the machine.. the computer dosin'.. the patients..

INTERVIEWER: err sorry.. err.. I.. I just need to know the.. usual process..
MADISON: Oh the usual process?
INTERVIEWER: yeah.
MADISON: well the usual process is… (cough) excuse me.. (cough).. parents call through the INR.…we listen to the answer phone message.. we take it down in the designated INR diary.. er.. we take out the INR prescription charts.. we write down.. what parents **have**.. called in..
MADISON: we give them to a paediatric registrar.. who does the dosin'… we then call parents back.. we tell them how much warfarin their child needs to take.. **and** when they need to re-test.
INTERVIEWER: err.. so is that process.. always straight forward? Like contacting the families and..
MADISON: nine times out of ten… i' only becomes as issue when you're tryin' to call a parent back.. and they're not answerin' their mobile.. or.. the mobile number says.. this phone **is** not available an' then you're in panic station thinkin' how am I goin' to get hold of these parents.. to tell them how much warfarin to give their child and when they're goin' to retest..and am I goin' to be able to get hold of them today..
INTERVIEWER: umhm. So.. and.. err.. how about the.. err.. families' compliance with.. with what.. you are prescribing?
MADISON: errr.. there.. are.. a handful of **families**.. **who**.. are not compliant.. ummmm and there are some families who will.. query what has been prescribed.. because they say they know their child better than the person… doin' the dosin' 'n actually for some of our parents.. there is a lot to be said for that.. because they do know their children.. much better.. and 'e final ones who… nine times out of ten the parents who do query the dose a' actually the parents who are **very** compliant.
INTERVIEWER: umhm… so do you find that.. like those parents who do their own dosing.. err.. do you find them right?
MADISON: errrrr… majority…majority of them.
INTERVIEWER: so they were right in..
MADISON: (at the same time) there's there's.. yeah.. the majority.
INTERVIEWER: so and they getting control of their.. uhm.. sorry..
MADISON: yeah.. 'n they only **ring**.. when there's actually **an issue** when.. it's out of range.
INTERVIEWER: umhm.. OK. So.. again back to the process of.. of warfarin initiation.. err.. right from the beginning of the treatment.. err.. of.. 'n.. when.. warfarin is.. prescribed.. when the patient first start that and your role in this process.
MADISON: my role?
INTERVIEWER: yeah.. right from the beginning.
MADISON: right from the beginnin'.. umm… I find tha' I have to teach the parentssss about.. umm… what warfarin is.. why it's used…things 'a can interfere with warfarin and… practical things.. umm… like….vitamin K is found in.. for example green vegetables..
MADISON: umm.. and…. teachin' them simply tha'.. warfarin is used to thin the blood...and…. there are certain food stuffs that contain vitamin K an' vitamin K **clots** your blood.. aaaannnd.. that… if like me.. you loved broccoli..
MADISON: it's all about consistency so….. dependin' on.. an'.. an' it's not to be used as tha' I always go' vitamin K an' I can' have it.. you can.. but it's about consistency so.. if you always have **a cupful of** broccoli.. e' know if.. if you like broccoli… decide

how much you gonna have.. is it gonna be half a cupful or is it gonna be a cupful.. and **stick to it**.. you can't do wha' I might do..
MADISON: an' that is at a weekend think Oh do you know what I fancy great big plate of bro' broccoli…'cause I have to teach them that.. your body has got used to… 3 milligrams let's say 3 milligrams of warfarin..
MADISON:… annnd.. if you star' havin'… a cupful of broccoli….. your body is goin' get used to that.. however.. at the weekend you think Oh do you know what.. I'm gonna have a great big bowl of broccoli.. we've just added more clotter….more vitamin K to your blood..
MADISON: so **therefore**.. your **INR**.. is goin' to be shorter.. so.. it will be.. umm… it takes.. less time to clot so it's goin' to be….umm.. around one… or..1.2.. or somethin'.. umm an' I find with the older patient**s** uhuhm.. we have to have conversations about…. alcohol.. because that too.. has an impact.
MADISON: and if you're goin' to have…umm… a pint o' beer.. you can always have a pint of beer… (cough).. excuse me.. (cough) what you can't do at the weekend is goin' to have a binge.. that down the pub at the weekend.. because that **too** will interfere.. with your.. warfarin levels.. so it's a lot of…teachin' and education.. bu'.. doin' that teaching.. and education in very practical ways.. so that they understand what you're talking about.
INTERVIEWER: aha. And.. errr.. how.. do you usually find the parents and older.. children..
MADISON: (at the same time) ummm.. I find..
INTERVIEWER: (at the same time) their response to that?
MADISON: (at the same) that it takes a while for that to register.. I think.. errr.. 'cause they have lots of the other things.. that they need to take on board.. with comin' to clinics and why they're comin' 'n.. you know bein' stressed out because they might need to be.. er.. admitted for a procedure or.. so.. it's constant ongoin' education.. that is wha' I find.
INTERVIEWER: OK. ummm.. and.. umm.. how often.. errrr.. do the INR monitoring usually takes.. take place? The INR monitoring and the dose changing.. how often…. does that happen?
MADISON: you mean as per patient?
INTERVIEWER: yeah.
MADISON: ummm.. for **me**.. I find that nine times ou' of ten.. Fontan patients.. are.. quite stable.. aannnd.. err… I think it's good that the majority.. are… tested once a month.
MADISON:… obviously there are occasions when… you know.. if they've had a growth spurt.. or… some parents have admitted that they've **forgotten** to give.... warfarin.. ummm.. annd.. that does actually have a massive impact that sometimes it can take… about **a week**.. or two before they get back to bein' stable..
MADISON: (cough)… I find… ummmm… patients who've got mechanical valve**s**… they're a bit more tricky.. errrr.. 'cause they seem to get tested… a lot…. and for some patients.. I can see.. that they need to be an' for some others I can't.. I jus'.. don't.. get.. why they've been tested so often.
INTERVIEWER: umhm. So is there a specific reason behind.. err.. being.. errr.. those patients with valves being less stable than those with Fontan?
MADISON: I have no idea 'cause I do try to find out I do try to ask why do you think..

MADISON: umm… and…. there is never…. a justifiable reason sometimes I mean.. the altercation is ‘cause parents ‘ve said ‘ve forgotten.. to give.. umm….. they never say we’ve had too much of broccoli or we’ve had.. too much alcohol I mean.. nine times ou’ of ten for some of my.. adolescent patients.. **I know**… that they’ve been drinkin’.. bu’ they are no’ admittin’ to i’.. bu’ you jus’ know tha’ they are.
MADISON: because over time you get er…. when you look back at the drug chart might ‘ve you think mmmm.…effff… it’s called good feeling..
MADISON: an’ I know you can’t.. er.. you know…that’s not fact is it? bu’ err…. for some patients.. they find it difficult to **admit** actually.. that’s wha’ I have been doin’.
INTERVIEWER: ummm…. So is their life style.. errr.. so apart from the life style the diet and alcohol and those stuff.. errrr.. er.. is there any like.. medical reason.. behind.. or a clinical reason behind those with valves being unstable?
MADISON: …… I don’t know the answer to that question to be honest..
MADISON: I know I know some kids have growth spurts… (cough).. bu’ I do’ I don’t know.
INTERVIEWER: aha. So.. errr.. what are.. usually the obstacles that you encounter in.. in getting the INR in range and in maintaining it in.. in the range?
MADISON: errrrr……. well it’s…… well I don’ know.. what I’ll call an obstacle.. I don’t know.
INTERVIEWER: some patients that are.. harder to maintain their INRs in the range or getting them into the range.
MADISON: (at the same time) there is quite a lo’.. there is quite a few.. mechanical.. valve patients..
MADISON: umm….. Sometimes it can be I can look at the chart an’ I can think I don’t know why that registrar ‘as…. done that dosin’…. an’ sometimes I might say why ‘ve you… done tha’.
MADISON: an’ they have their justification for i’.. I’m no’ a prescriber.. so.. you know.. it’s not down to me but I do question.. sometimes.. jus’ like I question some of the dosin’ from the.. from the.. errr.. the computer.
MADISON: ….. sometimes I think I don’t understand why they.. have been.. tested.. so often….. um ‘cause I think it’s cruel... to be tested… uhhuhm… every day… or every other day…. especially when children don’ like i’…
MADISON: umm….. but I do see the purpose and the point behind the study.. so.. you know.. once we’ve got **proof** then we we will… know in which direction we’re goin’ won’t we?
INTERVIEWER: yeah.. yeah exactly. Sooo.. yeah.. er.. so do.. do you encounter like some.. occasions when the patients are.. errr.. fluctuating in their INRs?
MADISON: yes. an’ when they’re fluctuatin’ we say to the parents why do you think it’s gone up or why do you think it’s gone down..
MADISON: parents will say well…. eefff… I told you tha’ the doctor the registrar who dosed i’.. you know I’ve said to you it would go.. up or down.. you know.. we shouldn’t ‘ve done such an’ such.. an’ that’s where sometimes parents actually… do know their child better.
INTERVIEWER: umhm. So is that regarding..
MADISON: an’ sometimes there is no consistency because.. you know.. we are all individual people. errr.. some registrars….. because they are all different.. they will have their own perspective an’ will see things you know…. some are.. much more consistent some aren’t.

INTERVIEWER: OK. So.. errr.. again back to my question.. errr… depending on the patient's general condition.. errr.. are there any times that their INRs are fluctuating.. apart from their diet or alcohol..
MADISON: (at the same time) alright..
INTERVIEWER: (at the same time) intake.
MADISON: you want that when they're on medication when they're on antibiotics.
INTERVIEWER: aha.
MADISON: yes..
INTERVIEWER: OK.
MADISON: yeah yeah yeah yeah….. I forgot abou' tha' yes sometimes.. bu' we know don't we? well I know.. tha' if they are on antibiotics an' I always tell parents.. tha' if your child has started antibiotics..
MADISON: you need to **ignore** the fact tha' we've told you to call to test in two weeks.. you need to test it… the day after the antibiotic has been started because we know there is going to be a massive change.
MADISON: an' when they ring **up**.. I say… umm… if I've told you to ring in two weeks but you've started…. at the end of this week antibiotics.. I need you to test the day after the antibiotic has been given… an' when you ring up you jus' **say**…. umm… my child's INR is such 'n such 'n the reason it's out of range is because he's commenced on amoxicillin 250 milligrams for so 'n so..
MADISON: so that we can **see**….. **why** there has been a deviation an' a change.
INTERVIEWER: umhm… OK. And.. yeah one more question please.. ummm… I do'.. know part fr'.. you'.. is.. your training is training on the INR machine.. errr..
MADISON: I was trained by a rep.
INTERVIEWER: aha. So.. yeah.. I mean training the patients on the INR..
MADISON: (at the same time) alright yeah.
INTERVIEWER: (at the same time) machine.. so.. errrrr… do you find that all families like to have the INR home INR.. testing.. machine?
MADISON: yes they do.
INTERVIEWER: ummm.. do they find it easy to use?
MADISON: errrr…
INTERVIEWER: or they prefer to come to the hospital to check their INRs?
MADISON: I think….. I think there is only a couple of patients.. who've…who've actually preferred to come to the hospital 'n.. 'n get checked.
INTERVIEWER: aha.. is that.. is..
MADISON: 'n I know a girl who lives in.. who lives down the road from here actually 'n she is a.. teenager 'n she could 've had.. the family could 've had an INR machine.. when she was.. umm.. **a child**.
MADISON: uhmuhm… ummm….. I know whenn errr…. 'cause she could 've had **a home**.. **machine**.. but she never wanted one….. never.. wanted one.
INTERVIEWER: so.. is there a specific reason behind that?
MADISON: errrr…. She jus' doesn' wan' 'o do i'…. she jus' wants to come here 'n have it done.
INTERVIEWER: it's more convenient for her.
MADISON: it's more convenient for her to come here 'n have it done she doesn't want one.
INTERVIEWER: alright. OK. Soo.. umm.. now errr… we move to the.. new dosing model..

MADISON: OK.
INTERVIEWER: so could you please let me know about your experience so far with the overall process.. of..
MADISON: (at the same time) Fontan patients fantastic.. it's really good.. errrr.. mechanical valve patients… umm.. I don' like i'.
INTERVIEWER: OK. Soo.. again I will ask is there a specific reason behind that?
MADISON: because they have to be tested much more often.
INTERVIEWER: so..
MADISON: one days two days..
INTERVIEWER: so.. OK.. so.. as compared with the.. with the frequency of.. err.. testing.. err.. according to the doctors'.. err.. prescription.. er.. is it comparable or different? do doctors usually do the same or… they tend to less…. err.. frequently testing them? the valve patients.
MADISON: …. hhhh… some patients it's abou' the same I think.. if there's been.. 'cause there are some patients who… who are not.. **stable** at all.. 'n it's very difficult to work out why they're not stable.…. Bu' for those tha' **are**…… I think.. the machine… still.. ask them to test…much more often.. than what the registrar does.
INTERVIEWER: OK. So this leads me to another question is that when the INR is just out of the range.. err.. I can see sometimes some of the doctors they give the same dose they.. still on the same dose for some patients..
MADISON: yeah.
INTERVIEWER: and give a long interval
MADISON: yeah.
INTERVIEWER: but for some others they change the dose and test in a shorter interval.
MADISON: I know they do.. uuhm..
INTERVIEWER: yeah.. so.. is there a specific reason behind that?
MADISON: … you'd have to ask the registrars 'cause I'm not the prescriber.. 'n I do say to them why 've you done tha'.. 'n they give me their give me their justification for it… sometimes I migh' agree with i' sometimes I don't.. bu' at the end of..
INTERVIEWER: (at the same time) so what type of justification that they usually..
MADISON: err.. because it was.. it was.. umm… higher there.. 'n then it went **low**.. and now it's just about.. to err.. to sort it out fast we jus' want to.. check it.. tomorrow.. just to see if it's gonna get back in range.
INTERVIEWER: umhm.. OK.. and are you convinced with their justification?
MADISON: sometimes…. Sometimes yes 'n sometimes no.
INTERVIEWER: aha. alright.
MADISON: an' it's very difficult to **answer**.. on a huge population of patients..right?
INTERVIEWER: umhm.
MADISON: to answer those.. questions properly you'd have to take.. an individual.. INR chart look at it.. look a'… everythin'… an' then… justify.
INTERVIEWER: OK.
MADISON: so.. you know.. broad spectrum **very difficult**.. **to give**.. **specific answers**.. because at the end of the day this is about individual..
INTERVIEWER: exactly.
MADISON: patient.. prescription.
INTERVIEWER: so the judgment depends on the general.. status of the..
MADISON: (at the same time) absolutely it's the individual..
INTERVIEWER: (at the same time) the general status..

MADISON: (at the same time) yeah.
INTERVIEWER: (at the same time) of the..
MADISON: (at the same time) of the child.
INTERVIEWER: (at the same time) of the specific child.
MADISON: (at the same time) yeah.
INTERVIEWER: yeah. OK.. errr.. so.. ummm… ummm.. would you.. could you please let me know about.. the **advantages** and **disadvantages** of this new model?
MADISON: errrrrr.. it's all the same to me 'cause I still have to listen to the messages… I still have to get somebody to prescribe i' 'n I still have to call the parents…. to errr… tell them… what need to take so.. it's no change for me..
MADISON: the only difference is.. instead of… umm.. puttin' theeeee.. chart.. in.. righ' I still need to put i' into the registrar's notes 'cause he still got to sign the prescription..
INTERVIEWER: of course yes.
MADISON: so for **me**.. there is.. you know.. it's no change whatsoever.
INTERVIEWER: umhm. So regarding.. errrr... the patients.. er.. so this..
MADISON: I think the Fontan patients.. err from conversations we've had like the.. computer model.. I think.. patients that I've had conversations with.. with the.. err.. computer dosin'..
MADISON: .. ummmm.. I think it's half 'n half.. half were OK with i' half think well.. I could do i' better myself (laugh).
INTERVIEWER: (laugh).
MADISON: (laugh).. do you know what I mean? So.. you know. We will see at the end of i' won't we? We will see wha' you've come up with.
INTERVIEWER: yeah of course and err.. are there any disadvantages?
MADISON: no because we're tryin' to make.. you know.. **this**.. **is**.. **a research** study.. isn' it? So the whole point of **it**.. is to make.. prescribin'.. on an **individual**.. **patient basis better**.
INTERVIEWER: exactly.
MADISON: so.. you know.. we **need** to be able to **prove**.. which is.. the best.. way to go don't we?
INTERVIEWER: exactly so that.. that is what I'm asking is there any something positive or something negative so that we can work on the positive make it better and.. try to..
MADISON: yeah well.. you know.. like I've said to you.. the positive for me is the Fontan patients it's good.. we need to get to the bottom of **why**.. for patients who've got mechanical **valves**..
INTERVIEWER: alright.
MADISON: why they are **still**.. why it's.. you know.. it's it's not quite a' straightforward.
INTERVIEWER: OK.
MADISON: right now is that because the patients… is it because of their diet.. I mean do we…have an in dep' conversation.. you know when I ask them why do you think it's ou' of range..
MADISON: there 've been some patients actually 'n the reason it's been ou' of range is because they've been on antibiotics.. bu' for some others… it's… I don't know why..
INTERVIEWER: OK.
MADISON: if they've had a massive growth spurt..

MADISON: have their parent forgotten to give the warfarin you know there is a whole…
INTERVIEWER: yeah.
MADISON: re'.. there is a whole…. host of factors.. where it could be..
INTERVIEWER: yeah.. yeah exactly so.. errr.. according to that during the usual phone call.. err.. how much... of information.. can you get..
MADISON: (at the same time) the problem **is**.. is tha'…. the message is left on the answer phone..
MADISON: so… you know… we can only do our best to tell parents.. if it's out of range can you tell us.. are they on antibiotics… have they had a growth spurt are they generally unwell..
MADISON: you know these are the things when we tell parents…. if they.. you know... are generally unwell.. vomitin' diarrhea… on antibiotics…. umm… even had a fall.. had a bang.. you know…. you need to test their INR… you need to ring on.. the answer phone.. 'n you need to tell us..
MADISON: if you're callin' out of the time sl'.. given time slot… why..
MADISON: when you're callin' parents **back**… so tha' you can have a conversation with them……. sometimes you **can't**.. because you have to leave a message on the answer phone 'n you have to write on the chart.. message left on answer phone..
MADISON: so sometimes you'd like to have **a dialogue**… bu' you know with the work load in the day.. we don't have a designated anticoagulation nurse..
MADISON: I think actually that this is a full ti' well.. at least a part time job we need to have somebody dedicated to it.. at least… every day..… because there are a huge amount of.. factors..
INTERVIEWER: of course.
MADISON: you know constant education… I think…..'n even now….. parents who've.. been usin' the INR machines for **a few years**.. when they come in every 6 months… to have their comparison check.. 'n you watch them prick the finger 'n the way they put in the blood.. on the strip.. you thinkin' to yourself that's not how I told you how to do it..
MADISON: so you have to rego back 'n say….. actually no.. don' keep doin' that.. because if you doin' that you're actually stoppin' the blood flow.. you need to gently.. just.. milk the finger.. so you ge' a nice drop o' blood.
MADISON: and.. if you're doin' tha'.. you know you haven' got an adequate supply.. you're no'….. to pu' your finger on top of the thing…. you are no' actually goin' to get much blood from there.. 'n if you do this 'n if you keep it by the side so.. you know.. it's constant constant constant education..
INTERVIEWER: exactly.
MADISON: so… as you give them information as you've taught them 'n they come back.. there is only so much of that actually they've retained.. which is why I think.. we need full time anticoagulation nurse..
INTERVIEWER: OK.
MADISON: who's goin' to be there all the time… to….. constant education.
MADISON: a parents have queries.. whatever..
INTERVIEWER: exactly.
MADISON: 'e can call you so.. they can call you up.. 'n you can… address the issue.
INTERVIEWER: exactly.. so how about those patients who do their own dosing.. errr.. what do you usually do in those circumstances?

MADISON: errrr… tell them tha' they shouldn' be doin' i'.
INTERVIEWER: OK is there any… errr.. like.. errr….. telling the… doctor that they are doing their own dosing so..
MADISON: yeah we do have conversations with the consultants about i'. 'n some..
INTERVIEWER: (at the same time) so is there a specific action?
MADISON: (at the same time) 'n some consultants 'n some consultants will say.. ah well actually they're doin' a better job.
INTERVIEWER: OK so they agree with that?
MADISON: yes some consultants do agree the patients.. do their own dosin'.
INTERVIEWER: and how about others?
MADISON: … some say no bu' there are some who are quite **happy..** 'cause they know the parents 'n they think well.. they can do.. just a good job.
INTERVIEWER: aha… OK and how do you see.. err.. the.. err.. the families' compliance with the computer dosing and the frequency of INRs?
MADISON: errrrr there's been a couple of parents who've.. said no I've no' given tha'. because it's gonna make it ou' of range.
INTERVIEWER: OK and about the frequency?
MADISON: errr yeah. Well actually no we've had one family.. we had to take them off because.. she was….. doin' her own thing.
INTERVIEWER: yeah.
MADISON: and…… I think she jus' got into our red from day one.
MADISON: to be honest. It was time I remember.. when I did the education program with her.. 'n I said to her that.. there are some families who.. do their own thin' 'n.. 'n she was like.. Oh that's terrible I'd never do that bla bla bla well she is a very one isn't she?
INTERVIEWER: (laugh) yeah.. OK so err.. do you recommend this errr….. computer dosing… model for other clinicians in the same area of congenital heart disease?
MADISON: I want to see the.. I want to see the results before I say anythin'.. I want to see the results.
MADISON: for Fontan patients I think it's fine.. bu' I want to see.. I want to see.. (bang bang bang on the desk)…. a hard evidence..
INTERVIEWER: (at the same time) (laugh)
MADISON: (bang bang on the desk).. in front of me before I.. I answer that question.
INTERVIEWER: OK.
MADISON: uhuh.
INTERVIEWER: errr.. so any.. err.. recommendations.. err.. so to make this.. model.. working better?
MADISON: errrrr let me see the evidence let me see what you come up with.
INTERVIEWER: and then you make your recommendations.
MADISON: (at the same time) and then I'll make my recommendations.
INTERVIEWER: Oh great.. brilliant.. err.. any other comments? That you would like to add?
MADISON: no.
INTERVIEWER: any other issue maybe.. that we have forgotten to discuss?
MADISON: errrrrrrr I think.. that weee… need to beee asking parents once a month to weigh their child.. and.. when we.. ring them up we say.. what was their last weight.

INTERVIEWER: yeah. This is O' yeah.. great.. that this is very important for the.. you know for the computer dosing.. but.. err.. we do not want to put much burden on.. parents because..
MADISON: (at the same time) I know..
INTERVIEWER: because it.. it will take..
MADISON: but.. it has an impact 'asn' i'?
INTERVIEWER: yeah of course.. we're trying.. we were trying and always trying our best to get the…. most updated weight..
MADISON: yeah. We do get it every six months.. when they do turn up.. for the comparison.
INTERVIEWER: exactly yeah.
MADISON: eeefff but I think for younger children…. I think it has a much more… im'.. much more impact..
MADISON: because because..
INTERVIEWER: (at the same time) definitely it has.
MADISON: we're testin' them more often are't we?
INTERVIEWER: definitely and we've got one of our patients we were requesting mum to do.. more frequent.. err weighing. but.. sometimes we get a weight sometimes we don't.. because..
MADISON: I know.
INTERVIEWER: yeah.
MADISON: 'cause.. yeah I know.
INTERVIEWER: we can't for'.. we can't..
MADISON: you can' any but try.
INTERVIEWER: yeah.. exactly.. so.. I've got one more.. more question soo.. errrr.. is that.. er.. the WATCH study.. err.. has put much pressure on you as cardiac liaison team?
MADISON: no.. not really.
INTERVIEWER: Oh brilliant.
MADISON: no. it's may my brain work though 'cause I'm thinkin' now why you've done tha'.. an' I have to look back.. and umm.. I try to work out.. why.. but no not really..
INTERVIEWER: alright.. brilliant. Thank you so much..
MADISON: you welcome.
INTERVIEWER: for your time.. for participating in the study.. for this valuable information..
MADISON: OK.
INTERVIEWER: and I will stay.. you know.. looking forward for your.. recommendations.. after the study.
MADISON: I'll read it.. an' I'll say if I agree or disagree.. an' you know me I'll be very honest (laugh)
INTERVIEWER: yeah of course.. of course.. yeah. And we want.. you know.. those.. because.. err.. this is theee.. thing that will make.. it.. work.. right.
MADISON: yeah.
INTERVIEWER: yeah
MADISON: yeah absolutely.
INTERVIEWER: thank you so much.
MADISON: it's OK Basma.

## Appendix 8: The study timeline