Chapter One
Introduction

1.1 Introduction

This chapter presents an introduction and background to the research, and identifies the gaps in prior research conducted in the study area. The research problem and the aims and objectives of the study are identified, resulting in the research question being formulated. The significance of the study, citing both theoretical and practical contributions, is outlined, and the reasons for the methodology adopted for the study are discussed. The chapter concludes with a presentation of the definitions adopted by the researcher for the thesis, the key assumptions made and an outline of the thesis.

1.2 Background to study

Warfarin has long been proven to be clinically effective in the primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism with prosthetic heart valves, for the prevention of acute myocardial infarct in patients with peripheral arterial disease and for the prevention of stroke, recurrent infarction or death in patients with acute myocardial infarction (The Medical Research Council's General Practice Research Framework 1998).

Most recently, randomised trials have shown that the incidence of stroke in patients with atrial fibrillation (AF) is reduced by 60-70% when treated with warfarin (Samsa et al. 2000). Because of an ageing population and an age-adjusted increase in the incidence of AF, the prevalence of the disease is ever increasing (Go et al. 2001; Ninio 2000).

The realisation of the clinical and cost effectiveness of warfarin in the treatment of thromboembolic disease, especially for reducing the risk of stroke in patients with AF, has given rise to a worldwide increase in the number of patients receiving warfarin (Murray 2003). In Australia, warfarin use has increased between 6-9% per annum in the last four years (Australian Pharmaceutical Index 2004).

However, despite this increase in its use, many clinicians continue to be reluctant to initiate their patients on warfarin (O'Connell et al. 2000). A recent study by Glazer et al. (2007) in the US revealed that only 59% of patients newly diagnosed with AF received

warfarin therapy, leaving a large percentage at a high risk of stroke. Likewise, several studies conducted in Australia have revealed that warfarin therapy remains underutilised, especially in the older population (Bajorek et al. 2002; Enis 1997; Jackson, Peterson & Vial 2004).

Conversely, warfarin is a potentially hazardous drug and can cause life-threatening haemorrhagic complications, with research indicating that patients are at the greatest risk of bleeding in the first few months of treatment (Campbell et al. 2001). Warfarin remains a difficult drug to dose due to its narrow therapeutic index (Ho & Brighton 2002) and its interaction with numerous drugs (Baker et al. 2004). Additionally, inadequate understanding by the patient and poor compliance, the presence of co-morbid conditions, patients of an older age (>75 years) and therapeutic activity that deviates from current best practice impact on the quality of anticoagulant control achieved (Campbell et al. 2001).

Several studies have shown that excessive anticoagulation with a prolonged International Normalised Ratio (INR) above 4.0 increases the risk of bleeding complications exponentially (Gallus et al. 2000; Levine et al. 2001; Panneerselvam et al. 1998). It has been predicted that approximately one in six INR values will exceed the desired range, particularly during the first few months of therapy and the resultant risk of a major bleed is estimated to be approximately 5% in the two weeks following an INR above 6.0 if warfarin is withheld and no other treatment is administered (Oden & Fahlen 2002).

In summary, based on the results of previous studies, there remain unresolved and controversial issues in the management of patients receiving warfarin therapy. Despite the evidence to support the benefits of warfarin use, especially in the treatment of AF, it remains underutilised, with the management of warfarin by doctors perceived as notoriously difficult (Bajorek et al. 2007). Reluctance to use warfarin therapy would appear to originate from concern regarding instability of the INR, especially elevated INR levels, which remain largely unexplained, and the risk of bleeding complications. Another explanation for doctors to show reluctance to initiate and manage patients on warfarin therapy has been attributed to poor patient compliance, especially among the elderly population (Kutner, Nixon & Silverstone 1991).

1.3 Research problem of study

While the most common and potentially devastating complication of warfarin therapy is that of haemorrhage, previous studies have indicated that there is a close relationship between the level of the INR and the risk of bleeding (Levine, Raskob & Hirsh 1989; Baker et al. 2004; Gallus et al. 2000). That is, an INR>4.0 places the patient at a greater risk of a bleed, with that risk rising sharply as the INR>5.0 (Baker et al. 2004). Furthermore, previous studies have also shown that the patient is at the highest risk of a bleeding event during the initial three months of therapy (Baker et al. 2004; Campbell et al. 2001; Linkins, Choi & Douketis 2003; Vadher, Patterson & Leaning 1997) and that INR control during the initial 30 days of treatment is predictive of subsequent INR control (Hylek & Singer 1994). Furthermore, several studies have suggested that older patients who incur an episode of over-anticoagulation take longer to return to a safe level, exposing them to potential bleeding complications (Fihn et al. 1996; Gurwitz et al. 1992; Hylek et al. 2001), and Koo et al. (2004) suggest that patients who incur an INR above the therapeutic range are associated with an increased mortality rate at 60 days after initiation.

Consequently, poor control of warfarin therapy may lead to increased morbidity and mortality, frequent doctor visits, longer and more frequent hospital stays and resultant increased health and hospital costs (Rigby, Clark & Runciman 1999). A secondary data analysis of a case series conducted in Western Australia by Burgess et al. (2005) revealed that in 2002 anticoagulants were the most common drugs implicated in adverse drug reactions (ADR) in people aged 60 years and over, causing hospitalisation. Furthermore, anticoagulants had undergone the greatest increase in ADRs since 1981. As a result of this data analysis, it was recommended that attention to clinical guidelines be urgently revised (Burgess et al. 2005).

It is highly unlikely that a new antithrombotic agent as effective as warfarin will be introduced in the near future. Furthermore, the increase in the need for the use of an effective oral anticoagulant, especially in the elderly population for the treatment of AF, will continue to rise, thus it is becoming more important to clearly define the safety issues surrounding warfarin. Key issues yet to be resolved include early management strategies, including frequency of monitoring, patient education and compliance, and maintenance of the International Normalised Ratio (INR) within the target range.

Furthermore, it would appear that there is a paucity of data available in the literature concerning the number of INR results above 4.0 during the initial five months of warfarin therapy in both the hospital and the community in the Australian setting. Additionally, there appears to be no available data on current trends in the management of patients receiving warfarin and whether improved INR control could be achieved. Therefore, the findings of this study will enable the researcher to identify gaps in the management of patients receiving warfarin therapy through the hospital/community interface from initiation for a period of five months, or less if warfarin therapy was ceased prior to this time. It will differentiate between problems caused by patient-specific factors and management-specific factors. In doing so, this research will provide data which will enable practising clinicians (doctors, pharmacists and nurses) to review their current practices and improve the process of care they provide accordingly. Additionally, this research will add to the body of knowledge concerning warfarin therapy practices and it will provide evidence-based knowledge to set policies in place for medical, pharmacological and nursing strategies.

1.3.1 Research aims and objectives

As this was a hypothesis generating research project, the aim was to review the current process of management of warfarin therapy, from initiation through the hospital / community interface for a period of five months or less if the warfarin was ceased prior to this time. This study seeks to identify gaps in the current system and provide a foundation for future research in the clinical setting.

The objectives of this study were as follows:

1. Determine the frequency of INR monitoring that currently occurs in both the hospital setting and in GPs' rooms during the initial five months of warfarin therapy.
2. Determine the number of episodes of over-anticoagulation during the initial five months of warfarin therapy, specifically the number in the first month compared with subsequent months.
3. Determine the number of major bleeds that occurred during the initial five months.

4. Assess the health status, the level of warfarin knowledge and degree of compliance of patients prior to an episode of over-anticoagulation.
5. Assess the concepts of medical management and current medical trends in the treatment of patients receiving warfarin.

These objectives led to the formulation of the following research question, to be addressed by the study: **Are episodes of over-anticoagulation potentially preventable or unforeseeable?**

In summary, while the researcher acknowledges that the findings of this study are not able to determine cause-and-effect relationships, the study will provide significantly important data to offer an insight into a complex and relevant phenomenon that in turn will allow the implementation of new strategies in the clinical setting and add to the body of medical and nursing literature.

1.4 Significance of study

When examining the literature pertaining to the management of the INR in warfarin therapy during the initial months of treatment, it was found that little research has focused on understanding the process of management of patients or the experience of patients receiving warfarin therapy in the real-world setting of the community. While there have been a large number of randomised clinical trials and large prospective cohort studies that have demonstrated the effectiveness of warfarin (Baker et al. 2004; Hirsh et al. 2003) and bleeding associated with warfarin (Fihn et al. 1993; Gallus et al. 2000; Landefeld & Goldman 1989; Levine et al. 2001; Panneerselvam et al. 1998), it appears there have been few exploratory, descriptive surveys that have followed the progress of patients receiving warfarin therapy in a real-life setting of the community that included data across a broad range of ages and clinical indications for warfarin in the Australian setting.

According to a report released by the Australian Institute of Health and Welfare (2006), which identified the extent and distribution of health in Australia, declining mortality has contributed to a significant and rapid increase in the population aged 65 years and over with an even more marked increase in the population aged 85 years or over. The report indicated that there were 2.6 million Australians aged 65 years or over, representing

13.1% of the total population, 110,000 persons aged 90 years or over and 5,178 centenarians, with an overall proportion of 1.5% of the population who were 85 years or over in 2005. According to this report, the ageing of Australia's population will result in an increasing number of people with disabilities from diseases that are more common in older ages (Australian Institute of Health and Welfare 2006). One such presenting health problem is AF, which has a prevalence of 0.4% in the general population but increases to 9% in persons over the age of 80 years (Ninio 2000). It is expected that the incidence of AF will continue to rise as the population ages. Ninio (2000) suggests that AF is the most common arrhythmia treated by cardiologists and general practitioners and although it is considered a benign arrhythmia, it is a major cause of morbidity.

The above data reveal that, not surprisingly, this is a condition of high prevalence that will continue to increase in the future and as such requires the resolution of issues associated with treatment, specifically, with warfarin therapy. Accordingly, this timely study emerged from the researcher's desire to examine the process of management of those patients being initiated on warfarin therapy in a real-life setting in order to identify and quantify gaps that exist in the current system. This exploratory, descriptive survey is the first study in Australia to provide multifaceted quantitative data that encompasses the frequency of INR monitoring, episodes of over-anticoagulation, bleeding events, the level of patients' knowledge and degree of compliance and current trends in the medical management of patients receiving warfarin therapy in hospital and community settings during the initial five months of treatment.

This research will make a significant practical contribution to the clinical setting by identifying and quantifying the gaps in the current system of warfarin management. It is anticipated that the findings of this study will allow the implementation of new strategies and policies in the clinical setting for doctors, nurses and pharmacists in the pursuit of effective and safe administration of warfarin therapy. An interdisciplinary approach, which would unite the goals of doctors, nurses and pharmacists and include aspects of management such as patient education, INR monitoring and medical management will be explored. The importance of the implementation of these strategies in the clinical setting must be acknowledged if the health care system is to manage the increasing number of patients requiring warfarin therapy, especially those diagnosed with AF, in the future.

This study will also make a significant theoretical contribution to the existing medical and nursing literature respectively. A review of the literature revealed a gap regarding the

prevention of episodes of over-anticoagulation in the Australian setting. Although the researcher acknowledges that the findings of this study will not be able to determine cause-and-effect relationships, it is anticipated that it will make a significant contribution towards improving the management of patients receiving warfarin therapy in the community.

Finally, the findings of this study will provide a basis for the formulation of future research questions and hypotheses that can be tested in subsequent analytical studies. While the concept of the prevention of episodes of over-anticoagulation is not new, little research has focused on developing risk strategies to reduce the incidence of such events. Specifically, research that is able to further explore the prevention of episodes of over-anticoagulation and stratify the risk variables that may significantly contribute to such events would be invaluable.

1.5 Overview of study methodology

This section provides an overview of the methodological framework for this study. Betty Neuman's Systems Model was used as the theoretical framework while the quantitative paradigm provided the methodological framework. The major concept identified in Neuman's model, based on the principle that a client is a complete system and that the subparts of physiological, psychological, sociocultural, spiritual and developmental factors are all interrelated (Neuman 1989 cited in Polit & Hungler 1999:113), allowed the researcher to adapt a holistic client approach to a complex phenomenon. The quantitative paradigm was chosen on the basis that it would deliver objective and orderly quantifiable data for statistical analysis for the purpose of adequately meeting the research objectives. An exploratory, descriptive survey design was utilised for the study as it would allow the researcher to gather accurate data in a practical and efficient manner and to achieve a 'snapshot' of the health experience of a population at a specified time.

The study included 294 patients consecutively identified to the researcher as having been initiated on warfarin who were thereafter followed up by their general practitioners (GPs), other health institutions or hospital clinics. Because the phenomenon under investigation is complex, data collection, which required 20 months to complete from September 2005 to April 2007, was multifaceted. The researcher acknowledges that because the duration of the data collection process was over an extended period of 20 months, the study verged

on a longitudinal survey. However, the extended period of data collection was essential in order to obtain the required sample size (n=300) to apply the necessary statistical analyses. Prospective and retrospective raw data were collected by the researcher and entered into a computer where code numbers maintained security of that data. The data included nominal data to indicate characteristics and variables of interest about the participants, and interval and ratio data to show rankings of events and subjects.

This study consisted of three major data collection stages. In the first stage data were obtained from the patient's medical records. The data included place of initiation of warfarin therapy by the patient, whether the GP received a discharge letter or not on the patient's discharge from hospital, whether the patient attended the haematology outpatient's department or not, the patient's telephone number, date of birth, gender and weight and the reason for commencing warfarin therapy. Data concerning current medications taken by the patient were also included as was the patient's medical history, including the history of previous warfarin therapy, when current warfarin therapy was commenced and pre-dose INR, haemoglobin (Hb), platelet and serum albumin levels. Additionally, data were collected regarding warfarin dosage, INR results, treatment delivered if the patient incurred an episode of over-anticoagulation, whether a new dose was administered after such an incident, whether the patient incurred a major bleed or not, whether a Hb level was attended to or not and the corresponding dates for all occurrences. A single episode of over-anticoagulation was defined as an INR>4.0 followed by two consecutive INR<4.0 within two weeks before the next INR>4.0 occurred.

The second stage of data collection included contacting each patient after discharge from hospital every 3-4 weeks for five months or less if warfarin therapy was ceased prior to this time to determine if they had incurred an episode of over-anticoagulation. If they had, they were asked a series of questions pertaining to their health status and compliance with therapy leading up to the episode. At the time of the initial episode of over-anticoagulation only, they were asked about their understanding of warfarin therapy in general. The patient was also asked to provide their warfarin doses, INR results and the corresponding dates if able to.

The third stage of data collection asked prescribing doctors both in the hospital setting and the community to complete a questionnaire. The questionnaire sought to obtain information regarding current medical management trends for patients receiving warfarin therapy. Lastly, on completion of the five months, and after consent had been gained from

the respective GP or health institution to access the patient's medical records, the accuracy of the data collected was confirmed and any missing data collected. A comprehensive account of the methodology employed is presented in Chapter Three.

The type of data obtained was considered appropriate to enable the researcher to apply the statistical analyses required to quantify the frequency of INR monitoring in both the hospital setting and in the GP rooms and determine the number of episodes of over-anticoagulation and major bleeds and the outcome of such events during the initial five months of treatment. The data also enabled the researcher to ascertain and quantify the current medical management trends in warfarin therapy, and patient's compliance, health status and degree of understanding of their warfarin therapy when an episode of over-anticoagulation occurred.

The Statistical Package for the Social Sciences (SPSS version 15.0) and Stata version 7.0 were used to carry out descriptive and inferential statistical analyses. A detailed summary of the data and the results of the statistical analyses are presented in Chapter Four.

1.6 Definitions

The following definitions are used throughout the thesis to maintain consistency.

Acenocoumarol (Nicoumalone; Sinthrome)

Acenocoumarol, an oral anticoagulant whose half-life is 10-24 hours, is more rapidly effective on the PT, has a shorter duration of action (than warfarin) of 2 days and whose maintenance dose is 1-8 mg/day is used to some extent in Europe, especially in France (Majerus et al. n.d. cited in Goodman Gilman et al. 1991:1322).

Activated partial thromboplastin time (aPTT)

aPTT has been widely acknowledged as a global procedure to monitor the effectiveness of heparin therapy, where the clotting time is prolonged in proportion to the level of heparin (Dade Behring 1999).

Albumin

Albumin constitutes the smallest plasma protein in the body. Albumin is produced by the liver and its function is to help maintain the water balance between blood and tissues and the regulation of blood volume by exerting osmotic pressure. They also transport proteins for fatty acids, some lipid-soluble hormones and certain drugs (Tortora & Grabowski 1996). Normal serum albumin levels have been defined as 31-44 g/L for this study (Open Architecture Clinical Information System (OACIS) 2006).

Allele

'One of two or more alternative forms of a gene that occupy corresponding loci on homologous chromosomes' (Glanze, Anderson & Anderson 1990:43).

Cytochrome P450 System

The hepatic cytochrome P450 system is an enzyme system in the liver which is responsible for the oxidation of foreign compounds (Tortora & Grabowski 1996).

Deep venous thrombosis

Deep venous thrombosis usually occurs in the lower limbs when activation of blood coagulation and platelet activation occurs resulting in the formation of thrombi. If the clot causes inflammation of the vessel wall, obstructs flow or embolises into the pulmonary artery, it can produce serious and acute problems (Hirsh & Fuster 1994).

Enzyme

An enzyme is 'a protein produced by living cells that catalyses reactions in organic matter. Most enzymes are produced in minute quantities and catalyse reactions that take place within the cells' (Glanze, Anderson & Anderson 1990:431).

Episode of over-anticoagulation

A single episode of 'over-anticoagulation' was defined as an INR>4.0 followed by two consecutive INR<4.0 within two weeks before the next INR>4.0 occurred (Westaway 2004).

Full Blood Count (FBC)

A full blood count provides information pertaining to the red blood cells, white blood cells and platelets in the blood and includes the following:

Haemoglobin g/L (115-160)
Hematocrit L (0.40-0.52)
Red Blood Count (RBC) $Lx10^{12}$/L (4.40-6.00)
Red Cell Distribution Width (RDW) % (12-15)
Mean Corpuscular Volume (MCV) fL (80-100)
Mean Corpuscular Haemoglobin (MCH) pg (27.0-34.0)
Mean Corpuscular Haemoglobin Concentration (MCHC) g/L (310-360)
Platelet count $x10^9$/L (150-450)

White Cell Count

Neutrophils $x10^9$/L (1.5-7.5)
Lymphocytes $x10^9$/L (1.0-5.0)
Monocytes $x10^9$/L (0.2-0.8)
Eosinophils $x10^9$/L (<0.4)
Basophils $x10^9$/L (0.0-0.1) (Open Architecture Clinical Information System (OACIS) 2006).

Genotype

'The genetic constitution of an individual' (Glanze, Anderson & Anderson 1990).

Haemoglobin (Hb)

'A substance in red blood cells consisting of the protein globin and the iron-containing red pigment heme and constituting about 33% of the cell volume involved in the transport of oxygen and carbon dioxide' (Tortora & Grabowski 1996:G-27). Normal haemoglobin levels have been defined as 115-160 g/L for this study (Open Architecture Clinical Information System (OACIS) 2006).

Haemorrhage

It has been suggested that the majority of classification criteria for a haemorrhage have been previously set against the background of patients with acute coronary syndrome and cardiac surgery where enoxaparin is administered only for five to six days, coupled with intensive monitoring. Thus, the classification criteria listed below were developed specifically for general medical patients who are anticoagulated on warfarin long-term (Gallus, Coughlin & Teague 2004).

Major haemorrhage

A major haemorrhage was defined as one of the following:

1. Clinically overt bleeding with a haemoglobin (Hb) drop of 2g/dL OR requiring transfusion of >or= to 2 units of Red Blood Cells (RBC) or whole blood (within three days of event).
2. Bleeding into critical organ (intracranial, retro peritoneal).
3. Bleeding causing or significantly contributing to death.
4. Bleeding necessitating re-operation.

Minor but clinically significant bleed

A minor but clinically significant bleed was defined as one of the following:

1. Overt source of bleeding with Hb drop of less than 2 g/L.
2. Epistaxis requiring intervention, i.e. packing, transfusion, medical review or lasting more than 24 hours.

3. Macroscopic haematuria which is persistent for more than 24 hours, associated with passage of clots, requiring intervention or further investigation.
4. Haematoma/bruising. Single haematoma greater than 20 cm^2, widespread bruising, clearly abnormal and either unexplained or out of proportion to expected (in setting of documented trauma or surgery).

Other bleeds

1. Hb drop of greater than 3 g/L in less than 35 days.
2. No overt bleeding.
3. Not due to rehydration or marrow failure (e.g. transfusional support for metastatic cancer, leukaemia).

Trivial/Minor not clinically relevant bleeding

Trivial/minor not clinically relevant bleeding was defined as:

1. Haemoptysis with pneumonia.
2. Haematuria with infection, indwelling catheter-related, microscopic haematuria.
3. Small, brief, self-limited epistaxis.
4. Rectal bleeding/spotting thought to be minor haemorrhoidal bleed or anal fissure bleed.
5. Bruising in keeping with clinical expectations (Gallus, Coughlin & Teague 2004).

International normalised ratio (INR)

The international normalised ratio is the standard method for monitoring oral anti-coagulation therapy. It converts the PT ratio measured with the local thromboplastin used into an INR, thus standardising the reporting (Hirsh et al. 2003). Normal prothrombin INR levels have been defined as 1.0-1.3 for this study (Open Architecture Clinical Information System (OACIS) 2006).

Isoenzyme

An isoenzyme is 'an enzyme that may appear in multiple forms, with slightly different chemical or other characteristics, and be produced in different organs, although each enzyme performs essentially the same function' (Glanze, Anderson & Anderson 1990:650).

Isomers

'Molecules that have the same molecular weight and formula but different structures, resulting in different properties' (Glanze, Anderson & Anderson 1990:651).

Liver Function Tests (LFTs)

Liver function tests are used to detect liver damage or disease and include the following:

Total protein-65-80 g/L
Globulins-22-39 g/L
Gamma glutamyl transpeptidase-0-40 U/L
Alanine Aminotransferase-0-50 U/L
Aspartate aminotransferase-0-40 U/L
Bilirubin-0-20 umol/L (Open Architecture Clinical Information System (OACIS) 2006)

Nomogram

'A graphic representation, by any of various systems, of a numeric relationship' (Glanze, Anderson & Anderson 1990:817).

Platelets

Platelets (thrombocytes) freely circulate in the blood in an inactive form. They initiate the first step in thrombus formation and form a platelet plug in haemostasis. In response to vascular injury, the von Willebrand factor interacts with glycoprotein Ib receptors located on the platelet surfaces, initiating the process of platelet adhesion (Brown 2006). Normal platelet count has been defined as 150-450 x 10^9/L for this study (Open Architecture Clinical Information System (OACIS) 2006).

Point-of-Care Monitoring (POC)

Small portable meters were developed in the mid 1980s that were 'capable of performing the PT test on finger-stick samples of whole blood utilising disposable test strips similar to those used by diabetics in the testing of blood sugar' (Matchar et al. 2005).

Pulmonary embolus

'Pulmonary embolus occurs by the migration of thrombi most commonly formed in the legs. The clot migrates to the pulmonary circulation and lodges in a vessel of the same size. The blockage prevents blood flow to the area distal to the clot. Unoxygenated blood begins circulating peripherally, resulting in hypoxemia' (Kidd & Wagner 1997:800).

Prothrombin time

The prothrombin time test is a coagulation test that is extremely sensitive to alterations in the vitamin K-dependent factors (II, VII and X). It is the most common test used to monitor the anticoagulant effect of warfarin (Lehne et al. 1990).

Racemic

'Pertaining to a compound made up of levorotatory isomers' (Glanze, Anderson & Anderson 1990:998).

Urea and Electrolytes (U/E)

Urea and electrolytes provide information pertaining to the body's chemical and electrolyte balance, bone, lipid, liver and renal function and include the following:

Sodium, potassium, chloride, bicarbonate, urea, creatinine, uric acid, eGFR (MDRD), anion gap, glucose, cholesterol, total protein, albumin, globulins, calcium, phosphate, magnesium, alkaline phosphate, gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), alkaline phosphatase (ALP), triglycerides (Open Architecture Clinical Information System (OACIS) 2006).

1.7 Key assumptions

The researcher recognises the existence of three key assumptions in this study. First, the researcher assumed that warfarin would be used for the treatment of primary and secondary thromboembolic disease for the duration of the study, and this was indeed the case. This assumption was made based on the researcher's experiences as a registered nurse for many years and information found in the literature. Although research is continuing on a worldwide basis, warfarin remains the only widely available oral anticoagulant, particularly in the Australian setting.

Second, the researcher assumed that an adequate sample size for the study would be obtained based on information gained from speaking with experienced personnel working in the study hospital and GPs in the community, and this assumption was also proved correct.

Third, this research was based on the assumption that nurses and doctors working in both the hospital and community environments would document all data correctly in the patient's medical records. It was also assumed that patients in the hospital setting who were prescribed warfarin did receive and take the medication as ordered.

1.8 Outline of thesis

The thesis is structured in five chapters.

Chapter One provides an introduction and some background to the research and identifies the research problem, the aims and objectives of the study, and the research question. The significance of the research is followed by a brief overview of the methodological framework, the definitions and the key assumptions of the study. An outline of the thesis concludes the chapter.

Chapter Two commences with the research question, followed by an introduction to warfarin therapy and a brief discussion of the kinetics and dynamics of warfarin, and the differences between the antithrombotic and the anticoagulant effects of warfarin. A comprehensive critical analysis of the relevant literature pertaining to the research and its aims and objectives is also presented in this chapter.

Chapter Three presents a detailed description of the research design and the methodology employed in the study. This includes a description of sample size, sampling strategy, data sought, data collection procedure and instruments used. This is followed by a description of the pilot study carried out, the methodological limitations of the design and the ethical issues encountered during the research. The chapter concludes with an overview of the data analysis techniques.

Chapter Four presents the data analysis techniques used and the results of the descriptive and inferential statistical analyses. Chapter Five presents a comprehensive discussion and interpretation of the findings, and concludes with recommendations and implications for future research.

1.9 Conclusion

In summary, this chapter has laid the foundation for the thesis. The chapter introduced the background to the research problem. The research aims and objectives and the research question were stated followed by the significance of the research, which identified both the theoretical and practical contributions of the study.

It is anticipated that this thesis will make a significant practical contribution to the clinical setting by identifying and quantifying the gaps in the current system of warfarin management and it will signify new strategies to be implemented. Those strategies specifically pertain to patient education and management strategies, including frequency of INR monitoring and administration of practical education to doctors.

Furthermore, this study will make an important theoretical contribution to the medical and nursing literature by providing an insight into very complex and relevant phenomena. The major findings of this study, which are that the initial month of warfarin therapy is the crucial month of treatment to avoid adverse events and that many episodes of over-anticoagulation are preventable, will provide the foundation for the formulation of hypotheses that can be tested in subsequent analytical studies.

An overview of the theoretical and methodological frameworks employed in the study were presented, as well as the definitions used in the thesis. Finally, the key assumptions made in the study were identified and an outline of the thesis was provided. The next

chapter will present a comprehensive review of the literature in relation to the research problem of this thesis.