Safer Anticoagulation Management In The Community: A Pharmacist-Led Approach

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Dedicated to my family and all my loved ones

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Abstract

Therapeutic monitoring in patients on warfarin is essential to enhance treatment efficacy with less complications. Medicine use review (MUR) enables individualised patient assessment to check and balance drug-related problems (DRPs). The aim of this research was to develop and implement a pharmacist-led MUR for patients on warfarin, assess patient knowledge and adherence, and address identified risks with prescribed treatment. Patients on warfarin attended a structured MUR session, during which baseline information to assess patient knowledge and adherence to warfarin treatment was collected. Point-of-care INR testing was performed with the CoaguChek®XS device. Medication reconciliation was performed to identify DRPs and to recommend clinical interventions. Patients were followed-up after two months to evaluate the impact of pharmacist intervention and degree of implementation of the pharmacist researcher's recommendations by the physician, pharmacist or patient. A total of 100 patients (56 male, 44 female; mean age 70.5 ±10.30, range 33-89 years) were assessed. Forty patients had an INR value outside the target range. The mean score in the warfarin knowledge test improved significantly from 7 to 10 points out of 12 post-intervention ($p<0.05$). The number of patients who were non-adherent to warfarin decreased from 25 to 11 post-intervention ($p<0.05$). Post-intervention a significant improvement in INR control was observed where time spent within therapeutic range increased from 69% to 80% ($p<0.05$). A total of 632 medications were reconciled (mean 6 ±2.76, range 1-16 medications/patient). A total of 481 DRPs (mean 5 ±1.83, range 0-9 DRPs/patient) were identified, out of which 40% were related to warfarin. Need for monitoring (30%), lack of compliance (20%) and need for patient education (19%) were the top three DRPs identified. Eighty-four percent of the pharmacist researcher's recommendations were

accepted, 20% of which resulted in changes to drug treatment. Ninety patients would be willing to use the proposed MUR service, if implemented. Improvement in patient knowledge, adherence, INR control and the high proportion of implemented recommendations suggest that pharmacist-led MUR improves therapeutic outcomes and patient safety.

Keywords: Anticoagulation clinic, drug-related problems, medicine use review, pharmacist-led clinic, warfarin

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List of Abbreviations

ACC	Anticoagulation Clinic
ACCP	American College of Clinical Pharmacy
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
ATR	Above Therapeutic Range
BNF	British National Formulary
BTR	Below Therapeutic Range
BP	Blood Pressure
DAA	Drug Administration Aid
DDI	Drug-Drug Interaction
DRP	Drug-Related Problem
DVT	Deep Vein Thrombosis
FIP	International Pharmaceutical Federation
INR	International Normalized Ratio
MDH	Mater Dei Hospital
MUR	Medicine Use Review
NHS	National Health Service
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PCNE	Pharmaceutical Care Network Europe
PE	Pulmonary Embolism
POCT	Point-of-Care Testing
POYC	Pharmacy of Your Choice
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guideline Network

SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Persons' Potentially Inappropriate Prescriptions
TTR	Time in Therapeutic Range
UK	United Kingdom
USA	United States of America
WTR	Within Therapeutic Range

Chapter 1

Introduction

1.1 Challenges associated with warfarin management

Since its clinical introduction in the 1950s, warfarin has been considered as a valuable oral anticoagulant due to its effectiveness in preventing and treating arterial and venous thrombosis (Campbell et al, 2001). Thromboembolic prophylaxis is indicated in patients with atrial fibrillation (AF), prosthetic valves, deep vein thrombosis (DVT), pulmonary embolism (PE), valvular heart disease and antiphospholipid syndrome (Ouirke et al, 2007; Tadros et al, 2010; Virjo et al, 2010; Keeling et al, 2011; Kirley et al, 2012; Guo et al, 2015; Focks et al, 2016). Warfarin is considered as a high-risk drug with a narrow safety margin potentially associated with serious adverse drug reactions and fatal medication errors (Campbell et al, 2001; Amuroso, 2004; Jackson et al, 2004; Ansell et al, 2008; Kimmel, 2008).

Warfarin has no standard dosing and various factors affect its pharmacodynamic and pharmacokinetic profile (Hirsh, 1991; Ansell et al, 2008; Turpie, 2008). Warfarin has a narrow therapeutic margin and requires regular monitoring to ensure that treatment is effective with the lowest probability of complications (Fareed et al, 2011; Tideman et al, 2015). The International Normalized Ratio (INR) is an important predictor of anticoagulation and each patient on warfarin must have the INR monitored regularly, with dose adjustments performed accordingly (Hirsh and Poller, 1994; Ansell et al, 2008; Wan et al, 2008). The beneficial outcomes of warfarin are directly dependent on INR control and the quality of dose management, since accurate dosing is crucial for safer and more effective anticoagulation (Murray, 2006; Young et al, 2011).

Warfarin management is complex and may be complicated by drug-drug and drug-disease interactions, genetic variability, lifestyle factors such as diet, smoking, alcohol consumption, and patient difficulty in understanding and managing warfarin dose changes (Jaffer and Bragg, 2003; Cho et al, 2011; Martins et al, 2011).

1.2 Approaches to improve the safety of warfarin therapy

Warfarin is often underused and sub-optimally managed due to its complexity (Bungard et al, 2009; Casciano et al, 2013). Optimising anticoagulation management ensures the efficacy and safety of warfarin treatment (Ryan et al, 2008). In 2009, the United States of America (USA) Joint Commission issued National Patient Safety Goals on anticoagulation treatment, stipulating the importance for healthcare systems to reduce harm associated with warfarin therapy (Joint Commission, 2009). These goals still feature in the 2015 Joint Commission Hospital Accreditation Program.[1]

Various approaches have been implemented to improve warfarin management, such as point-of-care testing (POCT), use of dosing algorithms, pharmacist-led anticoagulation clinics, medicine use review (MUR) and seamless warfarin management (Campbell et al, 2001; Franke et al, 2008; Kimmel, 2008; Ryan et al, 2008; Kheir et al, 2014). Patient-centered advanced pharmacy services in the community, where the pharmacist moves away from the traditional dispensing and counselling role to a more proactive role embracing pharmaceutical care, improve medication use and reduce drug-related problems (DRPs) (Hepler and Strand, 1990; Dugan, 2006; Kassam et al, 2013; Zolezzi, 2013; Allemann et al, 2014).

[1] The Joint Commission. National patient safety goals [Internet]. USA: The Joint Commission; 2015 [cited 2017 May 05]. Available from: URL: www.jointcommission.org/assets/1/6/2015_npsg_hap.pdf

1.2.1 INR monitoring by point-of-care testing

POCT devices have transformed INR testing from a demanding laboratory process to a more patient-oriented practice by presenting the opportunity to perform INR testing in the community setting (Murray et al, 2004; Huston, 2009, Ventola, 2014). POC INR testing devices are compact, reliable, easy to operate, provide immediate results and are adequate alternatives to conventional laboratory INR testing (Sickels et al, 1999; McBane et al, 2005; Lippi et al, 2008; Ryan et al, 2008; Shephard, 2010; Mifsud et al, 2013). Various studies have demonstrated the safety and reliability of POC INR testing devices (Ryan et al, 2008; Sobieraj-Teague et al, 2009; Yelland et al, 2010; Mifsud et al, 2013). Although some variability between POC and laboratory INR testing exists, studies confirm that in 60 to 78% of cases, the same clinical decision is taken when considering both results (Franke et al, 2008; Mifsud et al, 2013). Due to immediate access to INR results, POCT allows the health professional to perform prompt evaluation of the patient's anticoagulation status and enables face-to-face explanation of the INR result and dose adjustments needed according to warfarin dosing algorithms (Campbell et al, 2001; McBane et al, 2005).

1.2.2 Warfarin dosing algorithms

Warfarin dosing algorithms are tools to aid warfarin dose selection and improve appropriateness of warfarin dosing by allowing systematic dose adjustments (Bereznicki et al, 2007, Franke et al, 2008; Duff and Walker, 2010). Various studies have reported improved effectiveness and safety of warfarin treatment due to the reduction in supratherapeutic and subtherapeutic INR levels following the implementation of warfarin dosing algorithms in pharmacist-led anticoagulation clinics (Donovan et al, 2006; Dawson et al, 2012; Downing et al, 2016).

1.2.3 Pharmacist-led anticoagulation clinics

The introduction of pharmacist-led anticoagulation clinics enables pharmacists to engage in direct patient contact and take on a more proactive role in assessing a patient's anticoagulation management by carrying out POC INR testing, interpreting the INR result, adjusting and dispensing the required warfarin dose and providing patient advice[2] (Wiedenmayer et al, 2006). Pharmacist-led anticoagulation clinics have been established in various countries including the USA (Norton and Gibson, 1996; Chiqutte et al, 1998), the United Kingdom (UK) (Semple, 2001), South Korea (Choe et al, 2002), Kenya (Pastakia et al, 2010; Manji et al, 2011), New Zealand (Shaw et al, 2011), Canada (Rossiter et al, 2013) Saudi Arabia (Dib et al, 2014) and Japan (Yamada and Nabeshima, 2015).

Clinical practice guidelines have been established by the American College of Clinical Pharmacy (ACCP) (ACCP, 1992) and the Scottish Intercollegiate Guideline Network (SIGN)[3] to support the setting up of pharmacist-managed anticoagulation clinics and to highlight the importance and benefits of specialised anticoagulation clinics.

Pharmacist-led anticoagulation management significantly improves INR control, patient knowledge on anticoagulation, patient adherence to treatment, quality of life and clinical outcomes and decreases the frequency of adverse reactions, drug interactions, patient hospitalisation, emergency visits and costs (ACCP, 1992; To and Pearson, 1997;

[2]Urban R, Hirst L, Hildebrandt M. Pharmacists with a special interest in anticoagulation raise standards. Clinical Pharmacist [Internet]. 2009 [cited 2017 May 05]; 1:145. Available from: http://www.pharmaceutical-journal.com/careers/career-feature/pharmacists-with-a-special-interest-in-anticoagulation-raise-standards/10406241.article

[3]Scottish Intercollegiate Guideline Network (SIGN). Antithrombotics: Indications and management [Internet]. Edinburgh (Scotland): SIGN; 2013 [cited 2017 May 05]. Available from: URL: http://www.sign.ac.uk/pdf/SIGN129.pdf

Chiquette et al, 1998; Amuroso 2004; Bungard et al, 2006; Rudd and Dier, 2010; Saokaew et al, 2010; Lakshmi and Kirthivasan, 2013; Rossiter et al, 2013).

Accessibility of immediate INR results by POCT devices during a targeted MUR service allows for face-to-face discussions between the health professional and the patient (Ryan et al, 2008; Bounda et al, 2013; Jenzarli et al, 2013). Studies have shown that patient-centred pharmacist-led clinics improve INR management and are more likely to attain the desired patient outcomes compared to conventional care, since lack of interpersonal communication is associated with suboptimal INR control (Wilson et al, 2003; McLachlan et al, 2005; Shaw et al, 2011). Incorporating MUR in anticoagulation clinics aims to further improve treatment outcomes (Boswell and Bungard, 2015).

1.2.4 Medicine use review

MUR is a structured patient-centred service that may be considered as an extended consultation between the pharmacist and the patient, where the pharmacist performs individualised holistic evaluation and systematic review of the patient's medications with the objective to develop a pharmaceutical care plan (Dugan, 2006; Turner et al, 2007; Kassam et al, 2010; Blenkinsopp et al, 2012; Rathbun et al, 2012; Kassam et al, 2013). MUR is a diagnostic intervention to detect and solve DRPs and ensure that patients on chronic medications are provided with necessary monitoring and advice (Holden and Evans, 2009; Blenkinsopp et al, 2012). Pharmacists providing MUR review patient treatment to identify DRPs and assess patient knowledge and treatment adherence to be able to recommend clinical interventions to optimise therapeutic effectiveness, outcomes, safety and reduce medication errors (Lalonde et al, 2008;

Youssef, 2008; Child et al, 2011; Latif et al, 2011; Jokanovic et al, 2016). MUR services have been established in the USA since 2004, in England, Sweden and Wales since 2005, in Canada and New Zealand since 2007 and in Italy and Scotland since 2010 (American Pharmacists Association, National Association of Chain Drug Stores Foundation, 2005; Hellstorm et al, 2011; Blenkinsopp et al, 2012; Manfrin et al, 2015).

The increase in chronic treatment options and life expectancy has led to treatment complexity and polypharmacy (Viktil and Blix, 2008, Chan et al, 2012; Silva et al, 2015, Modig et al, 2016). DRPs limit beneficial effects of medications and pose significant health risks, since DRPs reduce treatment effectiveness, quality of life and may result in higher morbidity and/or mortality (Basheti et al, 2016; Daba et al, 2016). DRPs usually occur due to inadequate use of medication by the patient, prescribing errors and lack of necessary monitoring (Basger et al, 2015). DRPs may be classified as actual or potential, where actual DRPs are problems that have clinically manifested and potential DRPs are problems that have not yet manifested, however may lead to harm, if not resolved (Viktil and Blix, 2008).

The fundamental elements of patient-centered care are understanding treatment goals, providing patients with sufficient education and continuity of care while facilitating discussion between the patient and the pharmacist to allow patients to participate in treatment decisions (Latif and Boardman, 2008; Boswell and Bungard, 2015). MUR models may be refined to target specific chronic conditions and complex patient populations, such as patients suffering from asthma, diabetes mellitus, dementia and

patients taking high-risk medications, including non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, anticoagulants and antiplatelets[4,5,6] (Boswell and Bungard, 2015).

The narrow therapeutic index of warfarin and the complexity of anticoagulation management makes patients on warfarin ideal candidates for MUR services (Snella and Sachdev, 2003; Kneeland and Fang, 2010). Targeted MURs focusing on anticoagulation aim to view the patient holistically and to explore various approaches to improve treatment. Warfarin frequently causes DRPs and is associated with hospitalisations due to bleeding (Blix et al, 2004; Roughead et al, 2011). Hirri and Green (2002) identified warfarin as the cause for 1.5% of hospital admissions, most of which were preventable. The rate of major bleeding in patients 80 years or younger was 4.75 per 100 person years and 13 per 100 person years in patients older than 80 years (Hylek et al, 2007).

With regards to anticoagulation management, implementing a MUR service goes a step further than simply performing INR monitoring and ensuring that a patient is in the target INR range (Boswell and Bungard, 2015). Introduction of anticoagulation clinics incorporating MUR, is an improvement over traditional anticoagulation clinics, since the patient is managed holistically with special attention given to both anticoagulation and to concurrent therapies, such as antihypertensives, antidiabetics and antiarrhythmics, which increase the probability of treatment complications (Duff and

[4] Livingstone C. Targeted MURs for patients on NSAIDs. Pharm J [Internet]. 2011[cited 2017 May 05]; 287(1). Available from: http://www.pharmaceutical-journal.com/learning/learning-article/targeted-murs-for-patients-on-nsaids/11090832.article

[5] Pharmaceutical Society of Australia. MedsCheck and Diabetes MedsCheck consumer report template. [Internet] Australia; 2012 [cited 2017 May 05]. Available from: http://www.psa.org.au/download/ent/uploads/filebase/guidelines/3612-medscheck-guidelines-appendix-6.pdf

[6] Stimpson H. Targeted MURs for patients taking diuretics. Pharm J [Internet]. 2012 [cited 2017 May 05]. Available from: http://www.pharmaceutical-journal.com/learning/learning-article/targeted-murs-for-patients-taking-diuretics/11095881.article

Walker, 2010; Mendys et al, 2014). Through regular follow-up by a dedicated pharmacist, underlying factors which may be affecting the pharmacodynamic and pharmacokinetic profile of warfarin, and the patient's INR stability are identified (Kimmel, 2008; Boswell and Bungard, 2015).

1.2.4.1 Benefits of medicine use review

Interventions to identify and solve DRPs are essential, since 50% to 80% of DRPs are preventable (Hallas, 1996; Gurwitz et al, 2000; Lagnaoui et al, 2000). Medication reconciliation is the first step of MUR. Medication reconciliation ensures correct and comprehensive medication history, aims to reduce risks of medication errors and ensures that the patient is being prescribed the right drug and dose especially across care transition (Ptasinski, 2007; Hughes, 2012).

Specialised one-to-one anticoagulation clinics can improve medication use, therapeutic outcomes, patient safety, quality of life and cost-effectiveness by minimising risks associated with warfarin administration (Latif et al, 2011; Geurts et al, 2012; Kheir et al, 2014; Harrison et al, 2015; Manfrin et al, 2015; Sapkota, 2015). Close patient assessment allows identification and management of factors that increase the risk of bleeding or thromboembolic events, such as changes in disease status, poorly controlled hypertension, polypharmacy, co-prescribing of interacting drugs, non-adherence, nutritional status, social factors such as dementia, tendency for falls, reduced functional status, smoking and alcohol intake (Kagansky et al, 2004; Roughead et al, 2011). Individualisation of treatment through one-to-one sessions that focus on determining the warfarin doses according to INR value holistic assessment of patient's needs and inclusion of structured educational programmes with rigorous follow-up can result in

improved anticoagulation control (Rosendaal, 1996; Kimmel, 2008; Youssef, 2008; Ababneh et al, 2016). An improvement in treatment understanding and medication management has been observed in patients attending MUR sessions (Youssef et al, 2010; Sheridan et al, 2012; Dowling et al, 2016).

MUR allows structured educational interventions to improve patient knowledge and adherence through a focused, coordinated and consistent approach (Blenkinsopp et al, 2012). Tailored education involving face-to-face interaction and provision of written information is one of the best strategies to ensure patient education and empower patients to become more involved in medication management (Mayeaux et al, 1996; Beyth et al, 2000; Jenzarli et al, 2013; Briggs et al, 2005; Collins et al, 2014). Simple patient education supports patient behavioural changes towards medication management (Mendys et al, 2014).

Appropriate patient counselling in warfarin-treated patients is fundamental since poor understanding of treatment and modifiable factors affecting anticoagulation and lack of adherence to treatment and monitoring are the main reasons for therapeutic failure and adverse drug reactions (Newall et al, 2005; Dawson et al, 2011; Hanlon et al, 2013). Inadequate education on anticoagulation is linked to an increase in bleeding complications (Sawicki, 1999; Cohen et al, 2001; Tang et al, 2003; Kagansky et al, 2004; Stafford et al, 2011; Lane et al, 2015; Amara et al, 2016).

Patient education on anticoagulation therapy should be started prior to initiation of treatment to allow patients to be involved in treatment decisions (Roughead et al, 2011). A standard knowledge assessment tool assists health care providers in obtaining

objective evidence of the patient's level of anticoagulation knowledge, allows individualised patient counselling and facilitates continuous educational follow-up (Briggs et al, 2005). Standardised educational checklists help to set learning objectives, prevent omissions and assess patient knowledge (Duff and Walker, 2010).

Adherence to warfarin is dependent on compliance to the daily warfarin dose and on the frequency, timing and correct administration of doses, precautions related to consumption of alcohol and Vitamin K-containing food and necessary INR monitoring (Kneeland and Fang, 2010; Kim et al, 2011; Brown et al, 2012). One missed warfarin dose seven to ten days prior to an INR test may lead to suboptimal INR results (Kimmel et al, 2007; Jones and Lacombe, 2009; Ababneh et al, 2016). An improvement in medication adherence contributes to optimal treatment response, increase in quality of care and health care outcomes while reducing health care costs. Medication adherence tools are vital for the improvement of medication use and may contribute to enhancement in warfarin adherence. Resources to aid adherence include drug administration aid (DAA), pill boxes, personalised calendars showing the daily dose of warfarin and date of INR test, medication instruction sheets and medication reminder systems (Mendys et al, 2014).

1.2.4.2 Role of the community pharmacist in medicine use review

In 2008, a white paper entitled 'Pharmacy in England' was published in the UK outlining the importance of redefining pharmaceutical care provision. The white paper identified pharmacists as experts in medicine use and proposed greater use of the pharmacists' clinical skills to improve use of resources. Due to their accessibility and expertise in drug therapy, community pharmacists are in an ideal position to support

patients in drug therapy management to detect, prevent and resolve DRPs, at the transition between secondary and primary care[7] (McDonald et al, 2010; Williams et al, 2011; Lakshmi and Kirthivasani, 2013; Mossialos et al, 2013; Braund et al, 2014; Kuhn et al, 2015; Smith and Ferreri, 2016). Pharmacists have specialised training for the provision of pharmaceutical care, enabling them to perform a vital role in the prevention of medication errors and iatrogenic risks (Campbell et al, 2004; Avery et al, 2012; Silva et al, 2015).

At present, patient-pharmacist interactions at the community pharmacy take place during dispensing, where the pharmacist provides advice on the medication being dispensed. Time constraints and workload pressure do not usually allow in-depth discussions between the pharmacist and the patient. A one-to-one conversation during MUR increases the interaction with patients and provides pharmacists the opportunity to extend the counselling role (Latif et al, 2011).

The community pharmacist may be considered as an under-utilised health professional (Mossialos et al, 2015), with a report issued by the UK New NHS Alliance in June 2016[8] highlighting that the UK NHS has not yet managed to take advantage of the unique position and abilities of community pharmacists. The report suggests that there is a need for recognition of the value of the clinical role of community pharmacists, which may help in reducing demands on primary and secondary care. The report suggests that community pharmacists must assume a more proactive role and clearer

[7] Moffat T. Point-of-care testing in the community pharmacy. Pharm J [Internet] 2001. [cited 2017 May 05]; 267:267-8. Available from: http://www.pharmaceutical-journal.com/news-feature-point-of-care-testing-in-the-community-a-new-role-for-pharmacists/20004868.article

[8] New NHS Alliance. New NHS Alliance calls for community pharmacy 'forward view' [Internet]. Birmingham; 2016 [cited 2017 May 05]. Available from:http://www.nhsalliance.org/mediacentre/new-nhs-alliance-calls-community-pharmacy-forward-view-2/

strategies must be implemented by the NHS. The same initiative was adopted by the Canadian Society of Hospital Pharmacy[9] to improve medication-related outcomes through patient-centered care.

Provision of MURs add value to the community pharmacists' role by enhancing their professional status through advancement and extension of the counselling role with the aim to optimise therapeutic outcomes (Sheridan et al, 2012; Desborough and Twigg, 2014; Kheir et al, 2014). The MUR service has the potential to increase pharmacist personal satisfaction, improve time management skills, enhance the pharmacist-patient relationship, increase patient loyalty and strengthen relationships with other health professionals (Elrod et al, 2012). Enhancing the role of the community pharmacist is not an attempt to surpass the medical profession but to achieve multidisciplinary collaboration creating a team approach for the benefit of patients (Edmunds and Calnan, 2001; Smith and Ferreri, 2016).

1.2.5 Warfarin dosing by community pharmacists

Various studies show that pharmacist contribution in warfarin dose adjustment improves INR control (To and Pearson, 1997; Dager et al, 2000; Burns, 2004; Witt et al, 2005; Biscup-Horn et al, 2008; Downing et al, 2016). In a study by Dager et al (2000) in Minnesota, USA, dosing of warfarin by a pharmacist resulted in a decrease in INR results that were above 3.5. In a study by Witt et al (2005) in Colorado, USA, a 39% reduction in treatment-related complications was observed in warfarin-treated patients managed by pharmacists. The enhanced quality of care observed with warfarin dosing by pharmacists could be attributed to more conservative dosing by pharmacists (Ellis et

[9] The Canadian Society of Hospital Pharmacy. CSHP 2015 - Targeting Excellence in Pharmacy Practice [Internet]. Ontario; 2008 [cited 2017 May 05]. Available from: http://www.cshp.ca/cshp2015/

al, 1992; Dager et al, 2000). Pharmacist-led anticoagulation clinics improve continuity of care through provision of consistent treatment management (Ellis et al, 1992; Downing et al, 2016).

1.2.6 Seamless warfarin management

Seamless warfarin management contributes to safe and effective anticoagulation control. Seamless care enables the continuity of optimal patient care when patients are transferred from one healthcare setting to another to be managed by different health professionals (Simoens et al, 2011; Edwards et al, 2014). Provision of seamless care requires clear communication between health professionals on patient medication management. Effective standardised documentation of patient medication history, medication reconciliation and INR results ensures seamless communication and collaboration between health professionals to avoid unintentional discrepancies (Hägglund et al, 2007; Jones and Lacombe, 2009; Ozkaynak, 2012; Claeys et al, 2013). Lack of communication with patients about treatment adjustments and lack of patient education undermine provision of seamless care (Layson Wolf and Morgan, 2008; Claeys et al, 2013).

1.3 Local perspective: The situation in Malta

In Malta, warfarin is the most common prescribed oral anticoagulant since the novel oral anticoagulants (NOACs) are still relatively expensive and are not available on the national government formulary.

1.3.1 Role of the community pharmacist in the Maltese health care system

The Pharmacy of Your Choice (POYC) scheme was part of the Primary Health Care Reform proposal introduced in 2007 to decentralise the dispensing procedure of pharmaceutical products from government health centres to community pharmacies. The POYC scheme is a patient-centered service and increases patient accessibility to medication and medical information (Vella, 2010). A performance audit by the National Audit Office in 2012 established that the POYC initiative was an improvement over the older dispensing system.[10]

Through implementation of the POYC scheme, the community pharmacy became an integral part of the health care system and involvement of the community pharmacist in medication management increased. The POYC scheme enhanced communication between the patient and the pharmacist and created a niche that needs to continue to be explored by community pharmacists. Provision of advanced patient-oriented services may be achieved by focusing on the clinical potential of the community pharmacist and expanding the services being offered.

1.3.2 Anticoagulation monitoring system in Malta

Anticoagulation monitoring in Malta is centralised at the Anticoagulation Clinic (ACC) at Mater Dei Hospital (MDH), the general hospital in Malta or within government health centres. At present, the Maltese healthcare system provides two different INR testing methods; 1) laboratory INR testing and 2) INR testing using POCT devices.

[10] National audit office: Performance audit. An analysis of the pharmacy of your choice scheme [Internet]. Malta; 2012 [cited 2017 April 25]. Available from: nao.gov.mt/loadfile/4bd31498-d5ae-4261-bce2-60e7206d4a40

Each patient on warfarin has a yellow anticoagulation booklet, where all INR results and warfarin doses are recorded.

1.3.2.1 Laboratory INR testing

The laboratory-based INR monitoring system is still fragmented and lacks face-to-face communication between the clinician and the patient. A patients' INR is tested using a blood sample obtained by venepuncture, while dosing instructions are provided via telephone, followed by receipt of the prescription by postal mail a few days later. The current set-up may be inconvenient for the patient and may increase risks to patient safety due to misunderstandings in warfarin dose adjustments.

1.3.2.2 Point-of-care INR testing

INR testing using POC devices was implemented in Maltese government health centres in 2014. Patients with stable INR results have been transferred from laboratory INR testing to POC INR testing. Introduction of POC INR testing was an initiative towards individualising patient treatment since testing is performed by a nurse and a physician, and the result is available immediately, allowing the health professionals to provide face-to face advice and discuss dose adjustments with the patient. Junior physicians on rotation who are not specialised in anticoagulation usually perform warfarin dose adjustments and no pharmacist is currently present during the intervention.

1.3.2.3 Introduction of pharmacist-led anticoagulation clinics in Malta

In Malta, no infrastructure promoting MUR and no effective communication between patients, physicians and pharmacists to ensure seamless warfarin management exists. Introduction of a pharmacist within anticoagulation POCT teams may be of value for

assessment of modifiable variables affecting INR control. To date, both the patient's family physician and the community pharmacist are minimally involved in anticoagulation management.

Azzopardi (2010) and Mifsud (2013) concluded that 79% and 82% of patients respectively, were willing to start using a pharmacist-led anticoagulation service (Azzopardi, 2010; Mifsud, 2013). The findings in the study by Mifsud (2013) encouraged the development of guidelines to roll-out an effective framework for the implementation of a structured INR testing service within community pharmacies, combining blood collection, INR analysis with POCT devices and warfarin dose adjustments (Mifsud, 2013).

1.4 Rationale for the study

Introduction of MUR in the community pharmacy setting is a new concept in Malta. The increase in chronic treatment complexity highlights the need for regular MUR services to individualise patient assessment to detect and solve DRPs. The study models patient-centred MUR interventions through the lens of an anticoagulation clinic, since warfarin is a high-risk drug with a narrow safety margin, causing DRPs which may lead to patient hospitalisation.

This is the first study which evaluates the feasibility and outcomes of a patient-centred community pharmacist-led anticoagulation clinic providing MUR in Malta. The main study hypothesis was that an anticoagulation monitoring system, incorporating MUR led by a community pharmacist, improves anticoagulation therapy outcomes, increases patient knowledge and adherence, reduces medication errors, decreases incidence of

DRPs and improves patient quality of life and level of satisfaction with the service provided.

1.5 Aims and Objectives

The aim of the study was to develop and evaluate the impact of a pharmacist-led specialised anticoagulation service incorporating MUR to improve warfarin management in community practice.

The objectives were to:

i. Assess patient knowledge on warfarin before and after pharmacist intervention
ii. Evaluate adherence to therapy and INR monitoring before and after pharmacist intervention
iii. Perform a MUR session for each patient and individualise patient assessment to check and balance DRPs
iv. Compile an individualised pharmaceutical care plan for each patient
v. Assess DRPs identified and type of interventions recommended
vi. Assess patient attitudes and level of satisfaction regarding the proposed pharmacist-led anticoagulation service
vii. Determine the impact of clinical interventions recommended by the pharmacist researcher and analyse actions taken by the physician, patient or community pharmacist
viii. Evaluate the impact of pharmacist intervention on INR control
ix. Develop a clinical proposal for setting up a pharmacist-led specialised anticoagulation clinic incorporating MUR in collaboration with physicians.

Chapter 2

Methodology

2.1 Study design

A pre-post single-arm study design was selected to assess patients before and after pharmacist intervention, to evaluate the impact of the intervention. The study was classified as a prospective, interventional, practice-oriented primary research study where patients were assessed throughout a defined period of time, with data gathered and established findings used to design and implement a new service (Thiese, 2014). The methodology selected was a combination of quantitative and qualitative research. A pre- and post-intervention questionnaire (Appendix 1) and an 'Anticoagulation and Medication Profile' (Appendix 2) were developed to evaluate the effect of the MUR service and the impact of pharmacist intervention on the identified study outcomes (Section 2.2). The research tools were psychometrically evaluated.

Hundred patients were recruited from six community pharmacies. During the MUR sessions, an extended consultation between the pharmacist researcher and the patient was performed, where the researcher reviewed the patient's medication list, identified and classified drug-related problems (DRPs) according to the DOCUMENT classification system, provided clinical recommendations and addressed educational gaps. Baseline information collected during the MUR session (t=0) was compared to data collected two months after pharmacist intervention during the follow-up MUR session (t=1) (Figure 2.1).

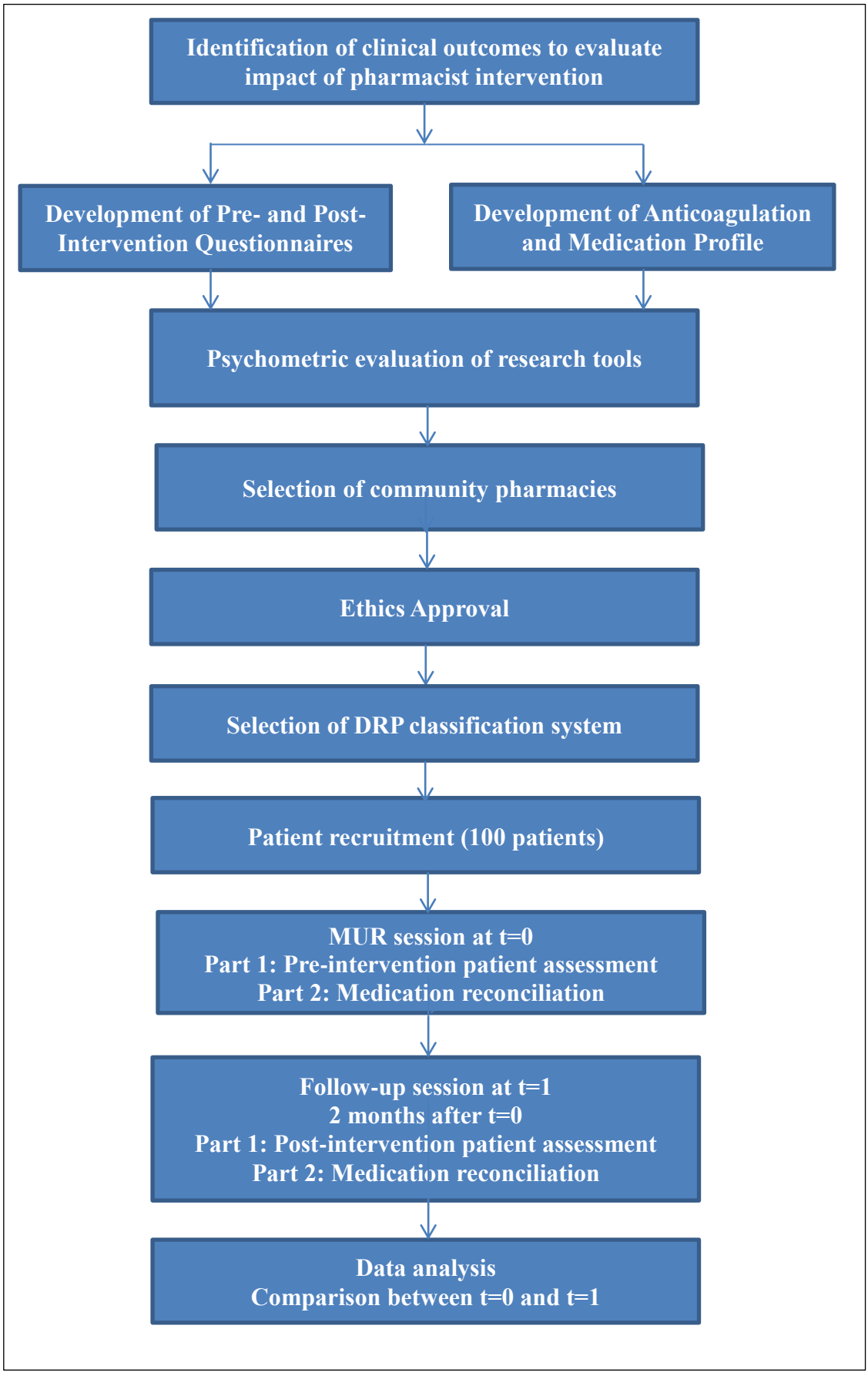


Figure 2.1: Flowchart of study design

2.2 Establishing study outcomes

Clinical and humanistic outcomes to evaluate the impact of pharmacist intervention were identified. The primary clinical outcomes were the number of DRPs identified by the pharmacist researcher and the number of clinical recommendations accepted by the physician, patient or community pharmacist (Campbell et al, 2004; Basheti et al, 2013; Manfrin et al, 2015). Other clinical outcomes included improvement in INR control and warfarin adherence. The humanistic endpoints included patient knowledge and understanding of anticoagulation therapy, effect of MUR on patient quality of life, level of patient satisfaction and perception of the proposed MUR service (Rosendall et al, 1993; Shaw et al, 2011; Tang et al, 2003; McLachlan et al, 2005; Huber et al, 2008; Roughead et al, 2011; Stafford et al, 2011; Obamiro et al, 2016).

2.3 Selection of community pharmacies for study

A chain of twelve community pharmacies was selected, from which the six pharmacies with the largest number of patients enrolled in the POYC scheme were included in the study. The pharmacies were selected from three different districts in Malta namely; Northern (Mellieħa, Naxxar), Northern Harbour (Qormi, Ħamrun, Pieta') and Southern Harbour (Paola).

The six community pharmacies hosting the study were visited to ensure availability of the required facilities to perform the proposed clinical service. All pharmacies were accessible to elderly patients and had a clinic available to perform the MUR consultation session in a private area with adequate lighting, a stable surface.

2.4 Development of research tools

A pre- and post-intervention questionnaire (Appendix 1) and the 'Anticoagulation and Medication Profile' (Appendix 2) were developed by the pharmacist researcher to standardise data collection during the MUR session and follow-up session.

2.4.1 Development of pre- and post-intervention questionnaire

Pre- and post-intervention patient questionnaires (Appendix 1) were designed to collect quantitative and qualitative data. The pre-intervention questionnaire was developed to be administered during the first part of the MUR session prior to pharmacist intervention, while the post-intervention questionnaire was to be administered during the first part of the follow-up session to evaluate the impact of pharmacist intervention after the MUR session. The questionnaire design was kept simple avoiding jargon so as, to avoid literacy and data collection problems. Both questionnaires were divided into four sections, three of which (Section 1, 2, 4) were identical in the pre- and post-intervention questionnaire to allow for direct comparison between patient responses (Table 2.1). A 'patient demographics data box' was included in the pre-intervention questionnaire to collect patient demographic data. The questionnaires were developed both in English and Maltese language and were designed to be conducted by the pharmacist researcher as a semi-structured interview. This technique is useful since it minimises incomplete responses, reduces the number of questions left unanswered, allows for clarification, avoids ambiguity and can be used in patients with visual problems or who are illiterate (Salek and Luscamba, 1992). Leading questions which prompt patients to answer in a definitive way were avoided to reduce bias. Both nominal and ordinal scale questions were included in the questionnaires, with nominal

scale questions used for categories without any quantitative value and numerical representations, while ordinal scale questions used to rank patient responses (Allen et al, 2007).

Table 2.1: Description of pre- and post-intervention questionnaire sections

Section	Pre-intervention questionnaire	Post-intervention questionnaire
1	Warfarin Knowledge Test: Assess knowledge on anticoagulation therapy and monitoring	
2	Warfarin Adherence Tool: Evaluate adherence to warfarin therapy and monitoring	
3	Assess patient perception of current anticoagulation service provided in government health centres	Assess patient perception of the MUR service provided by the pharmacist researcher during the intervention
4	Assess patient perception of the community pharmacist's role in therapeutic management and impact of pharmacist intervention on patient care with respect to anticoagulation therapy	

2.4.1.1 Section 1: Warfarin knowledge test

Section 1 of the questionnaires (Appendix 1) consisted of a warfarin knowledge test to assess patient knowledge on anticoagulation therapy and to identify education deficits requiring further counselling. Questions in the warfarin knowledge test were adapted from two previously validated knowledge assessment instruments (McLachlan et al, 2005; Zeolla et al, 2006; Obamiro et al, 2016). The questions included in the warfarin knowledge test covered important knowledge domains on anticoagulation, including warfarin indication, INR monitoring, effect of supra- and sub-therapeutic

anticoagulation, tablet identification, warfarin administration instructions, drug-drug interactions (DDIs), drug-food interactions and adverse drug reactions (ADRs).

2.4.1.2 Section 2: Warfarin adherence tool

The 'Warfarin Adherence Tool' in Section 2 of the questionnaire (Appendix 1) was adapted from a standard warfarin adherence tool, the 'Warfarin compliance-assessment scale' (Huber et al, 2008). Questions included in the adherence tool assessed factors affecting adherence and INR control, namely missed and extra warfarin doses, correct dosing, diet, alcohol intake and warfarin administration practices.

2.4.1.3 Section 3: Perception on current and proposed anticoagulation service

Section 3 of the questionnaire (Appendix 1) was designed to capture patient opinions regarding the current and proposed anticoagulation service and to evaluate data on patient experience. Previous validated questionnaires were adapted to the Maltese scenario and to meet the study objectives (Shaw et al, 2011; Mifsud, 2013, Bishop et al, 2015).

Section 3 was different in the pre- and post-intervention questionnaire. In the pre-intervention questionnaire, Section 3 assessed patient perception on the current anticoagulation monitoring service being provided in government health centres to allow identification of patient needs and concerns, methods used for INR testing and dose communication, and advice being provided at the government health centres. Questions incorporated in section 3 of the post-intervention questionnaire assessed patient views on their experience of the proposed pharmacist-led MUR service

including opinions on the quality of the service, willingness to start using the system, perceived benefits and improvements after the pharmacist-led MUR sessions.

2.4.1.4 Section 4: Patient perception of pharmacist competencies

Section 4 was identical in both the pre- and post-intervention questionnaire (Appendix 1). The questions included in Section 4 assessed patient perceptions of the pharmacist's roles and competencies and the influence of the pharmacist researcher's intervention on patient care and quality of life. Previous validated questionnaires were adapted to the Maltese scenario and to meet the study objectives (Shaw et al, 2011; Mifsud, 2013, Bishop et al, 2015).

Before psychometric evaluation, the pre-intervention questionnaire consisted of 43 questions and the post-intervention questionnaire consisted of 57 questions (Table 2.2).

Table 2.2: Questionnaire content before psychometric evaluation

Section	Title	Number of questions
1	Warfarin knowledge test	14
2	Warfarin adherence tool	11
3 (Pre-intervention)	Perception on current anticoagulation service provided by health centres	9
3 (Post-intervention)	Perception on proposed pharmacist-led anticoagulation service	14
4	Perception of the pharmacist's competencies and pharmacist's impact on quality of life	9

2.4.2 Development of 'Anticoagulation and Medication Profile'

The 'Anticoagulation and Medication Profile' (Appendix 2) was designed to record comprehensive and accurate patient medical history, reconciliation of the patient's medication list, identified DRPs and education points on anticoagulation. The purpose of the booklet was to record medical data and to provide written advice on warfarin treatment and facilitate communication between different health professionals.

The 'Anticoagulation and Medication Profile' is a nine page document, consisting of eight sections (A-H), presented in A4 format using Times New Roman font size eleven. The text was presented in a simple way to ensure that the content was easy to read, avoiding jargon while maintaining the integrity of the information presented. The sections were structured to facilitate collection of comprehensive patient data including patient demographics, medications and DRPs (Table 2.3).

Table 2.3 Sections of the 'Anticoagulation and Medication Profile' before psychometric evaluation

Section	Title	Content
A	Patient details and demographics	Personal details (name, age, gender), drug allergies, previous ADRs
B	Medical history	Past/current medical history
C	Social history	Smoking status, alcohol consumption
D	Patient medication profile	Comprehensive list of all chronic medications including; active ingredient, brand name, dose, formulation, dosage regimen, indication of use, administration instructions
E	Pharmaceutical care plan	Pharmaceutical care plan including; issue, recommendation, for consideration by
F	Information on warfarin	Summary of important points on warfarin therapy
G	Warfarin dose record	INR and warfarin dosing log
H	Warfarin compliance aid tool	Warfarin dosing calendar

The UK 'NHS Medicine Use Review Form'[11] and the 'MedsCheck and Diabetes MedsCheck consumer report'[12] developed by the Pharmaceutical Society of Australia were used as a guideline to develop Section D and E of the 'Anticoagulation and Medication Profile'. Section F was designed to reinforce the educational session provided by the pharmacist researcher during the MUR session. The National Patient Safety Goals issued by the USA Joint Commission[13] were used as a guideline to identify the main points to be included to ensure comprehensive anticoagulation patient education (Tuiskula et al, 2011). The counselling points were summarised from validated patient booklets used by the NHS in the UK[14] and by the Department of Health in Western Australia.[15] The key points included were the importance of follow-up INR testing, diet restrictions, any potential ADRs, drug interactions and compliance issues.

Accurate, up-to-date and evidence-based data was presented as bullet points with each statement containing only one idea. Jargon was avoided and short sentences were used to improve readability of the text. Statments were written in the active voice using a conversational style (Kitching, 1990; Hoffman and Worrall, 2004).

[11] NHS. Community Pharmacy Medicines Use Review & Prescription Intervention Service [Internet]. UK; 2012 [cited 2017 May 05]. Available from: http://psnc.org.uk/wp-content/uploads/2013/07/mur20form20v220_final.pdf

[12] Pharmaceutical Society of Australia. MedsCheck and Diabetes MedsCheck consumer report template [Internet]. Australia; 2012 [cited 2017 May 05]. Available from: http://www.psa.org.au/download/ent/uploads/filebase/guidelines/3612-medscheck-guidelines-appendix-6.pdf

[13] The Joint Commission. National Patient Safety Goals Effective January 1, 2015 [Internet]. USA; 2015 [Cited 2017 May 05]. Available from: http://www.jointcommission.org/assets/1/6/2015_NPSG_HAP.pdf

[14] The National Patient Safety Agency. Oral Anticoagulant Therapy. Important information for patients. UK; 2007 [cited 2017 April 26]. Available from: www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=19112

[15] Government of Western Australia. Department of health. Living with warfarin. Information for patients [Internet]. Australia; 2007 [cited 2017 May 05]. Available from: http://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Quality/PDF/Living-with-Warfarin.ashx

Section G of the booklet focused on anticoagulation management. Patient awareness of the warfarin dose to be administered and the date of the next scheduled INR test was ensured by including a table to record changes in INR values and warfarin dose according to date. This table was adapted from the table found in the patients' yellow anticoagulation booklet. Two innovative features were included to aid patients in taking the appropriate warfarin dose, namely fields indicating 'Dose change' and 'Dose administration instructions'. Section H consisted of a warfarin calendar dosing aid to be completed by a pharmacist indicating the warfarin dose to be taken on each day and the next date of the INR testing appointment.

2.5 Validation of pre- and post-intervention questionnaire

A two-round Delphi technique was selected to validate the pre- and post-intervention questionnaires. A twelve-member expert panel was selected on the basis of their knowledge and experience in anticoagulation management. An invitation email explaining the aims of the study and what participation in the validation process entails was sent to potential panel members. The multidisciplinary expert panel who agreed to participate included two cardiologists, one neurologist, one general practitioner, two community pharmacists, two clinical pharmacists, two pharmacists working in academia and two lay persons, one of which was prescribed warfarin in the past.

A validation tool consisting of structured statements to assess the relevance of each question included in the pre- and post-intervention questionnaire and the level of agreement with options provided for each question was developed. The validation exercise involved rating the relevance of each question on a Likert scale from 1 (Not relevant) to 5 (Highly relevant) and the level of agreement with options provided for

each question on a Likert scale from 1 (Highly Disagree) to 5 (Highly Agree). A box for any suggestions for amendments or explanation of the expert panel's comments was included.

The tool for Delphi validation round I consisted of 66 statements to assess question relevance and 58 statements to assess the level of agreement with options given for each question. The questionnaire for round I of the validation exercise was disseminated to the expert panel by electronic mail. The panel members were asked to return the validated questionnaire within two weeks. All twelve members of the validation panel completed round I of the validation exercise and returned their feedback. The comments and suggestions provided by the panel in round I were analysed. The ratings for each question were collated in Microsoft Excel® 2010. A mean rating score for each question was calculated. The mean score gave an indication of the panel's opinion regarding the relevance and level of agreement with options provided in each question. Questions were accepted as valid if a mean score of 4.5 or higher out of 5 was obtained.

The mean score of the 66 statements assessing the relevance of the questions was 4.58 (range 3.9-4.91), with 14 statements obtaining a mean rating score less than 4.5. The mean score of the 58 statements assessing the level of agreement with options given for each question was 4.42 (3.50-4.83), with 26 statements obtaining a mean rating score less than 4.5.

The recommendations and mean scores obtained in validation round I were considered to develop the tool for round II of the validation exercise. The expert panel commented that the questionnaires were well-designed. Questions or options that obtained a mean

rating score less than 4.5 were removed, rephrased or replaced according to the suggestions of the expert panel to improve the quality of the questionnaires enabling collection of accurate data.

Six out of the twelve panel members commented that the options of the second question in Section 1 ‘Warfarin may be used to:’ were not comprehensive since there was no option stating that warfarin may be indicated in atrial fibrillation for prevention of thrombus formation, therefore the option reading ‘treat people that already have a blood clot’ was modified to read ‘that already have a thrombus (blood clot) or to prevent a thrombus (blood clot) from forming in patients at risk’. The panel suggested a change to question 7 in Section 1 that read ‘Are you aware of the importance to always remind a health professional that you are on warfarin?’ from a True or False question to a question asking ‘Which health professional should be informed that you are taking warfarin?’ with four options. This question was modified to ensure that patients are aware of situations where they need to specify that they are taking warfarin.

A modification which was suggested by eight of the twelve panel members was to improve question 9 in section 1 ‘Which of the following interferes with how warfarin works?’ by including the options food, vitamins and herbal supplements. The panel suggested removal of question 14 in section 1 since a similar question was already included. This question was replaced with a new question reading ‘When is it safe to take a medication that potentially interacts with warfarin?’. Eight panel members stated that question 10 in Section 2 reading ‘Does your consumption of Vitamin K-containing foods change throughout the week?’ may confuse patients since patients may not be

aware of foods contain Vitamin K, hence the question was modified to read 'Does your consumption of leafy green vegetables vary from week to week?'.

In Section 3 of the pre-intervention questionnaire question 2 was the only question to score less than 4.5, and was removed since it was similar to a question asked in the previous section. Questions 2b, c, e, and f in Section 3 of the post-intervention questionnaire were also removed. An important suggestion was to modify all the questions in Section 4 from binomial statements (yes or no) to Likert Scale type questions with options from 1 (Highly Disagree) to 5 (Highly Agree), since this will allow better comparison between responses provided pre- and post-intervention.

The tool for validation round II consisted of 58 statements to assess the relevance of each question and 50 statements assessing the level of agreement with options given for each question. The same procedure used in validation round I was applied in round II. All twelve panel members participated in round II and a consensus on the final version of the questionnaires was reached.

The mean rating scores obtained in validation round II improved. The mean score of the 58 statements assessing the relevance of the questions was 4.73 (range 3.9-4.91), with only 1 statements obtaining a mean rating score less than 4.5. The expert panel stated that question 1 in section 2 'Adherence assessment tool' which read 'What warfarin dose are you currently taking?' was not relevant since the dose of warfarin changes frequently. Although the question scored 4.41, no amendments were performed since the objective of the question was to assess if the patient recalls his/her current warfarin dose. A mean score of 4.67 (range 4.25-4.83) was obtained for the 50 statements

assessing the level of agreement with the options given for each question in the questionnaire, with only one question scoring less than 4.5. This question (Section 1 number 12) was removed.

The questionnaires (Appendix 1) after validation consisted of four sections. The pre-intervention questionnaire consisted of 48 questions including 31 nominal scale questions with the number of options provided ranging from 2 to 5, 14 ordinal scale questions and 3 open-ended questions. The post-intervention questionnaire consisted of 47 questions including 26 nominal scale questions with the number of options provided ranging from 2 to 4, 16 ordinal scale questions and 5 open-ended questions (Table 2.4).

2.6 Questionnaire translation

The validated questionnaires were forward translated from English to Maltese language by the pharmacist researcher. This was essential to ensure comprehensibility by all the study population. The translation was performed in a systematic way to ensure that the Maltese version was authentic to the validated English version since inadequate translation may affect the validity of the questionnaire.

A qualified linguistic translator from the Department of Maltese at the University of Malta was contacted to assess the quality and orthography of the Maltese translation. The translator carried out a back translation, where the Maltese version of the questionnaire was translated back to English to assess presence of any discrepancies between the two versions and to ensure that both questionnaires were equivalent in terms of wording, cognitive level and content. A satisfactory agreement between both versions was obtained.

Table 2.4: Questionnaire after validation

Section	Question	Description	Type of Question
Demographics		Age	Ordinal
		Gender	Nominal
		Level of education	Ordinal
		Duration of warfarin treatment	Ordinal
1	1	Patient perception of their warfarin knowledge	Ordinal (Likert scale)
	2	Warfarin Indication	Nominal, 4 options
	3	Indication for INR testing	Nominal, 4 options
	4	Risks of high INR results	Nominal, 4 options
	5	Risks of low INR results	Nominal, 4 options
	6	Main side-effects of warfarin	Nominal, 4 options
	7	Importance of reminding health professional on warfarin intake	Nominal, 4 options
	8	Distinguish between different warfarin strengths	Nominal, 4 options
	9	Warfarin interactions	Nominal, 4 options
	10	Warfarin-food interactions	Nominal, 4 options
	11	Optimal time for warfarin administration	Nominal, 4 options
	12	Managing missed warfarin dose	Nominal, 4 options
	13	Warfarin- drug interactions	Nominal, 4 options
2	1	Current warfarin dose	Open ended
	2	Who prepares medication	Nominal, 3 options
	3i	Days when warfarin dose missed	Nominal, 'yes' or 'no'
	3ii	Number of missed doses	Nominal, 4 options
	4i	Days when extra warfarin dose administered	Nominal, 'yes' or 'no'
	4ii	Number of extra doses	Nominal, 4 options
	5	Difficulty in changing warfarin doses	Nominal, 'yes' or 'no'
	6i	Intake of wrong doses	Nominal, 'yes' or 'no'
	6ii	Reason for intake of wrong dose	Open ended
	7i	Non-compliance with INR testing	Nominal, 'yes' or 'no'
	7 ii	Reason for missing INR testing	Nominal, 'yes' or 'no'
	8	Consumption of Vitamin K-containing food	Nominal, 4 options
	9	Alcohol consumption	Nominal, 4 options

Section	Question	Description	Type of Question
3 (Pre-intervention)	1	Where INR is checked	Nominal, 4 options
	2	Method of blood sampling	Nominal, 2 options
	3	Method of dose communication	Nominal, 4 options
	4	Preferred method of dose communication	Nominal, 5 options
	5i	Initial counselling on warfarin therapy	Nominal, 'yes' or 'no'
	5ii	Health professional responsible for counselling	Nominal, 4 options
	6	Satisfaction with current service	Ordinal (Likert scale)
	7	Satisfaction with ongoing counselling on anticoagulation	Ordinal (Likert scale)
	8i	Need for improvement of current anticoagulation service	Nominal, 3 options
	8ii	Suggestions for improvement of current anticoagulation service	Open ended
3 (Post-intervention)	1	Provision of new information by pharmacist	Nominal, 3 options
	2a	Satisfaction with duration of MUR session	Ordinal (Likert scale)
	2b	Better understanding of treatment after MUR	Ordinal (Likert scale)
	2c	Satisfaction with printed material provided	Ordinal (Likert scale)
	2d	Willingness to make use of MUR service	Ordinal (Likert scale)
	3	Perception of how pharmacist can contribute in patient's holistic care	Nominal, 3 options
	4	How did MUR help patient	Open ended
	5	Anything that bothered the patient	Open ended
	6	Any additional suggestions	Open ended
4	1	Inconvenience of warfarin dosage adjustments	Ordinal (Likert scale)
	2	Effect of warfarin on quality of life	Ordinal (Likert scale)
	3	Pharmacist can manage warfarin treatment safely	Ordinal (Likert scale)
	4	Pharmacist contributes to better INR control	Ordinal (Likert scale)
	5	Pharmacist able to improve patient warfarin knowledge and confidence in handling anticoagulation treatment	Ordinal (Likert scale)
	6	Useful to discuss treatment with pharmacist	Ordinal (Likert scale)
	7	Pharmacist performing dose changes	Ordinal (Likert scale)
	8	Pharmacist reviews medication	Ordinal (Likert scale)

2.7 Reliability testing of the questionnaire

Reliability of the questionnaires (Appendix 1) was assessed using the test-retest reliability method. Ten patients on warfarin were recruited by convenience sampling and were asked to complete the validated questionnaire twice, via a semi-structured interview (t=0) and after two weeks (t=1).

The responses provided at t=0 and t=1 were coded and statistically analysed. The Kappa test was used for 13 questions with a nominal scale, while the Kendall Tau test was used for 11 questions with an ordinal scale. For both statistical tests, the null hypothesis specified poor test-retest reliability and was accepted if the p-value exceeded the 0.05 level of significance, while the alternative hypothesis specified satisfactory test-retest reliability and was accepted if the p-value was less than the 0.05 level of significance. Due to lack of variation between responses in 11 of the questions the Kendall Tau test and Kappa test could not be used and percentage agreement between the responses provided by the patients at t=0 and t=1 was assessed and reliability was confirmed if 70% to 100% agreement was achieved.

Thirteen questions with a nominal scale had satisfactory test-retest reliability according to the p-value of the Kappa test (p-value <0.05, range 0.000-0.035). The 11 questions with an ordinal scale had satisfactory test-retest reliability according to the p-value of the Kendall Tau test (p-value <0.05, range 0.000-0.003). A test-retest percentage agreement between 70% and 100% was obtained for the rest of the questions. Since all questions showed satisfactory test-retest reliability and internal consistency, the questionnaire was confirmed to be reliable with no modifications needed and could be disseminated (Appendix 1).

2.8 Validation of 'Anticoagulation and Medication Profile'

The 'Anticoagulation and Medication Profile' booklet (Appendix 2) was also validated using a two-round Delphi technique. The same multidisciplinary twelve-member expert panel who validated the questionnaires was invited to validate the 'Anticoagulation and Medication Profile'. A validation tool was developed consisting of eight structured statements to assess the relevance of each section included in 'Anticoagulation and Medication Profile' and another eight structured statements to assess the level of agreement with the contents of each section. Validation involved rating the relevance of each section on a Likert Scale from 1 (Not relevant) to 5 (Highly relevant) and the level of agreement with the information presented in each section on a Likert scale from 1 (Highly Disagree) to 5 (Highly Agree). The panel members were asked to provide feedback and suggestions in the box for recommendations.

Ten out of the twelve panel members returned their feedback. The panel members agreed that the booklet was an effective tool to record patient medication history, improve patient knowledge and improve adherence to medications and INR testing. The mean rating score of the eight statements assessing the relevance of each section was 4.66 (range 4.1-4.9), with only one statement scoring less than 4.5 out of a maximum of 5 (Section G). The mean rating score of the eight statements assessing the level of agreement with the content of each section was 4.48 (range 4-4.8), with four statements scoring less than 4.5.

All sections that obtained a mean rating score less than 4.5 were removed or modified according to the suggestions of the expert panel with the aim to improve the content and presentation of the 'Anticoagulation and Medication Profile'. Two panel members

suggested inclusion of patient name on each page and inclusion of date of completion on the medication profile. Two experts suggested that Section B 'Medical History' should be modified from a series of empty fields to input the patient's medical history, to a defined list of common medical conditions from which the pharmacist may select the relevant conditions. The heading of Section C 'Social history' was changed to 'Lifestyle factors', since three panel members suggested that 'smoking' and 'alcohol consumption' do not portray the complete social history of the patient. For Section E 'Pharmaceutical care plan', five panel members commented on the lack of relevance of the column 'Consideration by' in the 'Pharmaceutical care plan' table, however this was not removed since it was deemed essential by the pharmacist researcher to allow identification of which health professional should consider the recommendation identified by the pharmacist and would facilitate data analysis.

An important modification was removal of Section G 'Warfarin dose record'. This was recommended by six members of the panel since Maltese legislative requirements do not permit dosing adjustments to be performed by a pharmacist, inclusion of the section may confuse the patients. Since all patients are in possession of an official yellow anticoagulation record booklet which is used in government health centres to record INR results and warfarin doses, this section was not needed.

Following implementation of the amendments suggested by the expert panel in round I the same ten panel members were asked to participate in round II of the validation exercise. The tool for validation round II consisted of seven statements to assess the relevance of each section and seven statements to assess the level of agreement with the content of each section.

A consensus on the final version of the 'Anticoagulation and Medication Profile' (Appendix 2) was obtained since all sections obtained a mean score of 4.5 or more out of a maximum of 5. A mean score of 4.8 (range 4.7-4.9) was obtained for the statements assessing relevance. A mean score of 4.61 (range 4.5-4.8) was obtained for the statements assessing the level of agreement with the contents of each section. The validated version of the 'Anticoagulation and Medication Profile' (Appendix 2) was translated into Maltese by the researcher and back translated to English by the same qualified linguistic translator from the Department of Maltese at the University of Malta who translated the questionnaires. After validation, the final version of the 'Anticoagulation and Medication Profile' consisted of eight pages and was divided into 7 sections (A-G).

2.9 Ethics approval

The 'Request for Approval of Human Subjects Research' which contained a detailed description of the aims and methodology of the study together with a copy of the covering letters (Appendix 3), consent forms (Appendix 4), questionnaires (Appendix 1) and the 'Anticoagulation and Medication Profile' (Appendix 2), all in English and Maltese and approval from the owner of the community pharmacies hosting the study, were submitted for review. Approval to conduct the study was granted by the University of Malta Research Ethics Committee in April 2016 (Appendix 5).

2.10 Selection of drug-related problem classification system

An extensive literature review to identify available DRP classification systems that can be used during pharmaceutical care processes was performed. DRP classification systems formalise, standardise, support and avoid issues while identifying DRPs since

they set concise and clear definitions of each DRP category, hence simplifying the identification, coding and documentation of DRPs and recommendations for any clinical interventions (van Mil et al, 2004; Bjorkman et al, 2008).

Various classification systems were identified, all designed for use in different health settings, using different structures, terminologies and with several alterations and adaptations (Bjorkman et al, 2008, Williams et al, 2011; Adusumilli and Adepu, 2014; Basger et al, 2015). The identified classification systems include the; Helper and Strand system (USA) (Helper and Strand, 1990), Cipolle et al system (USA) (Cipolle et al, 1998), Westerlund version 5 (Sweden) (Westerlund et al, 1999), Apoteket AB (Sweden) (Apoteket et al, 2001), Granada-II (Spain) (Consensus Committee, 2002), version 6 of Pharmaceutical Care Network Europe (PCNE)[16] (Europe), Individualised Medication Assessment and Planning (iMAP) (USA) (Crisp et al, 2011) and DOCUMENT classification system (Australia) (Williams et al, 2011).

The DOCUMENT classification system was selected to be used for the study since it was designed to be used in the community pharmacy setting, is well-constructed, easy to use and focuses on both the DRPs and interventions to resolve them (Basger et al, 2014; Basger et al, 2015). The DOCUMENT classification system is considered as an improved classification system developed using the types of DRPs identified by the Hepler and Strand system and PCNE classification[16] (Helper and Strand, 1990; Williams, 2013). Another reason for selection of the DOCUMENT classification was the inclusion of a category on the need for monitoring, which allows the pharmacist to

[16]PCNE. PCNE Classification for Drug-Related Problem [Internet]. UK; 2010 [cited 2017 May 05]. Available from:http://www.pcne.org/upload/files/11_PCNE_classification_V6-2.pdf

assess monitoring requirement for therapeutic and toxic effects of medications (Hsu et al, 2016).

The DOCUMENT classification system focuses on all aspects of drug therapy, including prescribing, dispensing, medication administration, patient knowledge, compliance to therapy and need for monitoring. The DOCUMENT classification system satisfies the five major requirements of a well-constructed classification system outlined by Schaefer (2002). The classification is validated, has a clear definition of all DRP categories, has an open hierarchical classification, focuses on the drug-use process and outcomes and separates the problem from the cause.

The DOCUMENT system consists of eight main categories, broadly defining DRPs and thirty subcategories, specifically defining the type of DRP. The main categories are: 1) drug selection (D), 2) over or underdose (O), 3) compliance (C), 4) undertreated (U), 5) monitoring (M), 6) education and information (E), 7) not classifiable (N) and 8) toxicity or adverse reaction (T). Each category includes between one and eight subcategories (Table 2.5).

Table 2.5: DOCUMENT classification system

Code	Category	Subcategory
D	**Drug Selection** (DRPs associated with the choice of drug)	Duplication
		Drug interaction
		Wrong drug
		Incorrect strength
		Inappropriate dosage form
		Contraindications apparent
		No indication apparent
		Other drug selection problem
O	**Over or underdose** (DRPs associated with drug dosing)	Prescribed dose to high
		Prescribed dose to low
		Incorrect or unclear dosing instructions
		Other dose problems
C	**Compliance** (DRPs associated with medication administration and adherence)	Under-use by consumer
		Over-use by consumer
		Erratic use of medication
		Intentional drug misuse
		Difficulty using dosage form
		Other compliance problem
U	**Undertreated** (DRPs associated with conditions that need to be managed)	Condition undertreated
		Condition untreated
		Prevention therapy required
		Other untreated indication problem
M	**Monitoring** (DRPs associated with monitoring needs to ensure safe and efficient treatment)	Laboratory monitoring
		Non-laboratory monitoring
		Other monitoring problem
E	**Education and Information** (DRPs related to educational gaps and requests for information)	Consumer requests drug information
		Consumer requests disease management advice
		Other education or information problem
N	**Not classifiable**	Clinical interventions that cannot be classified under another category
T	**Toxicity or adverse reaction**	Toxicity, allergic reaction or adverse effect present

Reproduced from: Pharmaceutical Society of Australia. Standard and guidelines for pharmacist performing clinical interventions [Internet]. Australia; 2011 [cited 2017 May 05]. Available from: http://www.psa.org.au/downloads/practice-guidelines/pharmacists-performing-clinical-interventions-guideline.pdf

2.11 Familiarisation with clinical screening tools

The Beers Criteria (American Geriatrics Society, 2015) and Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria (O'Mahony et al, 2015) were consulted prior to initiation of the MUR service (Pretorius et al, 2013). Drug informatics sources including the BNF (2016) and Summary of Product Characteristics (SPCs) were consulted to assist the pharmacist researcher in providing evidence-based recommendations during the MUR sessions.

The Medscape drug interaction checker[17], a free peer-reviewed web-based interaction checking tool, was selected to identify and classify potential DDIs. The tool has been used in other studies (Sivva et al, 2015, Badiu et al, 2016) and allows various drug combinations to be inputted, including prescription, OTCs and herbal supplements. The interaction checker classifies the interactions according to their clinical significance, namely as 'serious', 'moderate' or 'minor'.

2.12 Patient recruitment

Patients were introduced to the study by the managing pharmacists of the participating community pharmacies who distributed the covering letters to eligible patients when visiting the pharmacy to collect their medications through the POYC scheme. The covering letter outlines the study objectives and what patient participation in the study

[17] Medscape. Medscape drug interaction checker [Internet]. USA: New York; 2017 [cited 2017 April 18]. Available from: http://reference.medscape.com/drug-interactionchecker

entailed (Appendix 3). Patients 18 years or older and receiving warfarin through the POYC Scheme for the past three months were eligible to participate in the study. Patients younger than 18 years, with cognitive impairment, pregnant, suffering from antiphospholipid syndrome, home-bound or over 90 years of age were excluded.

Convenience sampling was used to recruit the study population, where patients meeting the inclusion and exclusion criteria were selected on the basis of willingness and availability. Patients interested to participate in the study were asked to leave their contact details for the pharmacist researcher to be able to contact them to set an appointment for the MUR session. All data collection took place following informed written consent. Patients were informed that they will be invited to attend two clinical sessions; the MUR session (t=0) and the follow-up session (t=1). An appointment with the pharmacist researcher was set up at the patient's community pharmacy for the MUR session and patients were requested to bring the yellow anticoagulation booklet and all documents related to their medical and drug history for the session.

2.13 Framework for medicine use review and follow-up session

A framework to enable standardisation of pre- and post-MUR sessions was developed (Figure 2.2). Each clinical session was divided into two parts, part 1 and 2. Part 1 of the MUR session consisted of a pre-intervention patient assessment, where the pre-intervention questionnaire (Appendix 1) was used to assess patient baseline knowledge on anticoagulation, adherence, satisfaction with the current anticoagulation management system and patient perception of pharmacist's competencies. Retrospective INR results were recorded to assess INR control for each patient. An INR test was performed using

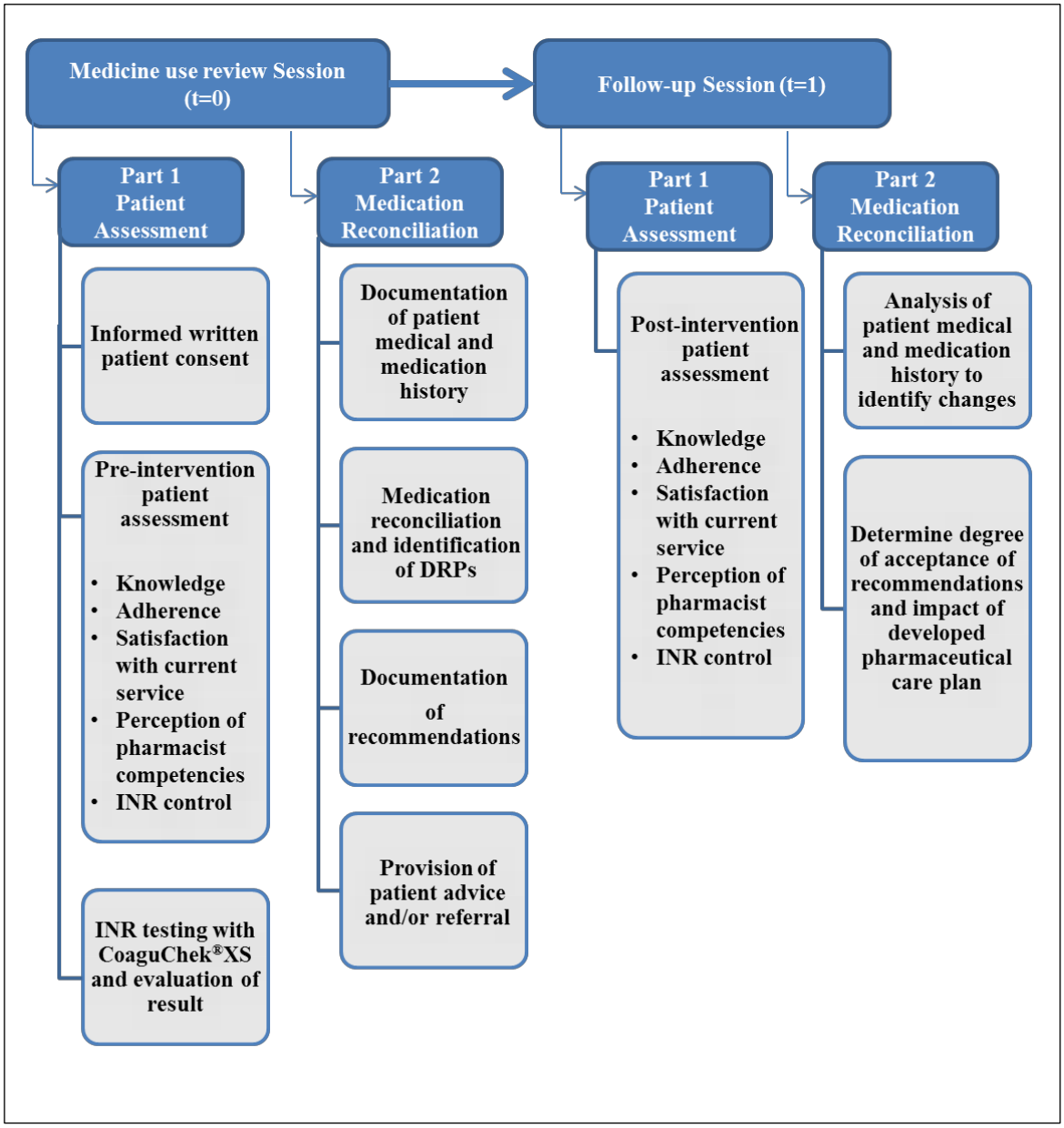


Figure 2.2: Framework for the medicine use review and follow-up session

the POCT CoaguChek®XS device. Pharmacist intervention was carried out during the second part of the MUR session, where the pharmacist researcher documented the patient's medical and medication history on the 'Anticoagulation and Medication Profile' (Appendix 2), performed medication reconciliation to identify DRPs, recommended clinical interventions and provided necessary advice and referrals.

The follow-up session was performed after two months by the same pharmacist researcher and similarly to the MUR session, during the first part of the follow-up session post-intervention patient assessment was performed. In part 2, medication reconciliation was performed to identify the number of accepted and unsolved recommendations (Figure 2.2).

2.14 Pharmacist-led medicine use review session

The MUR session was conducted in a designated clinic in the pharmacy to ensure privacy and avoid disruption. The proposed service was explained and the patient was informed step by step regarding the process to be followed. The patient was assured that data collected and personal information will be used solely for the purpose of the study and that all details will remain strictly confidential.

Patients were advised that the service being provided was an adjunct to their usual visits to the physician and INR testing performed at the ACC or at the health centre and not as a substitute. Patients were informed that they was free to opt out of the study at any time and that this would not affect treatment rights or care in any way and asked to read and sign the consent form. The content of the consent form was read by the pharmacist researcher for patients with literacy problems.

2.14.1 Patient assessment

During the first part of the MUR session, the pre-intervention questionnaire (Appendix 1) was completed to capture the level of patient knowledge on anticoagulation, level of adherence to treatment and patient perception of the current anticoagulation service and proposed service. The questionnaire was administered by the pharmacist-researcher as a semi-structured interview, which allowed the pharmacist researcher to interview patients in a flexible but guided way to ensure collection of standardised qualitative and quantitative information.

2.14.2 INR testing

The POCT CoaguChek®XS device was used to check the INR of each patient. INR testing was included during the MUR session to assess the feasibility of a pharmacist performing POC INR testing during the service. The guidelines compiled by Mifsud et al (2013), 'Pharmacist-led Anticoagulation Monitoring Service', were followed during the INR testing procedure to ensure good clinical practice and to obtain a reliable INR result.

2.14.2.1 External quality assessment for CoaguChek®XS

CoaguChek®XS has an in-built quality control system integrated into the device and test strips. For each INR test, the system runs a two-level quality control, which checks for test strip integrity and meter performance. This system allows for excellent quality assurance and does not require manual calibration since calibration is performed automatically.

In order to confirm the accuracy of the CoaguChek®XS and ensure that the device was providing reliable and valid INR results throughout the study, a comparative analysis method was developed between the CoaguChek®XS device and the CoaguChek®XS PRO device available at the POCT Department at MDH. The CoaguChek®XS PT Control, a liquid quality control that complements on-board system checks and assesses the reproducibility of the CoaguChek®XS PRO POC device was tested by both POCT devices. The results obtained with both devices were compared to assess the level of agreement. Reliability was confirmed if the accepted control test performed with the CoaguChek®XS PRO device and INR test with the CoaguChek®XS device produced the same INR result. A control test was carried out for each new tube of CoaguChek® XS test strips used during the study. All results obtained in the external quality assessment for CoaguChek®XS were satisfactory and 100% agreement was observed in the four control tests (Table 2.6).

Table 2.6: CoaguChek®XS control test results

Date (2016)	**Result with CoaguChek®XS**	**Result with CoaguChek®Pro**	**Level of agreement** (%)
15/04	1.9	1.9	100
16/06	1.8	1.8	
21/07	1.8	1.8	
24/08	1.8	1.8	

2.14.2.2 INR testing procedure

A total of 100 INR tests were performed with the CoaguChek®XS during the MUR sessions. Each INR result obtained was interpreted by the pharmacist researcher to determine whether the patient's INR was within range and whether the patient required

a change in the warfarin dose. The appropriate recommendation was provided after considering the previous INR result, the date of the next scheduled INR test at the government health centre, confirming that the patient was taking the correct warfarin dose and evaluating any changes in medication, lifestyle, diet or comorbidities.

Patients who obtained a result within the therapeutic range were advised to remain on the same warfarin dose and attend for the next scheduled INR test at the government health centre. Patients who obtained an INR value which was out-of-range required a dose adjustment. Since to-date, Maltese legislative requirements do not permit dosing adjustments to be performed by a pharmacist, patients were referred to the government health centre for further INR assessment. No referral was performed for patients who had a dose change five days before the MUR session or had the INR test scheduled in the next three days at the government health centre.

2.14.3 Medication reconciliation

A formalised medication reconciliation process was developed to be followed during the MUR session to establish a pharmaceutical care plan for each patient (Figure 2.3). A proactive approach was used throughout the interview to encourage patients to engage in a two-way discussion. The structured approach to perform MURs for patients taking warfarin developed by Youssef (2008) was followed. The pharmacist researcher focused on the patient's overall care, medications and anticoagulation management.

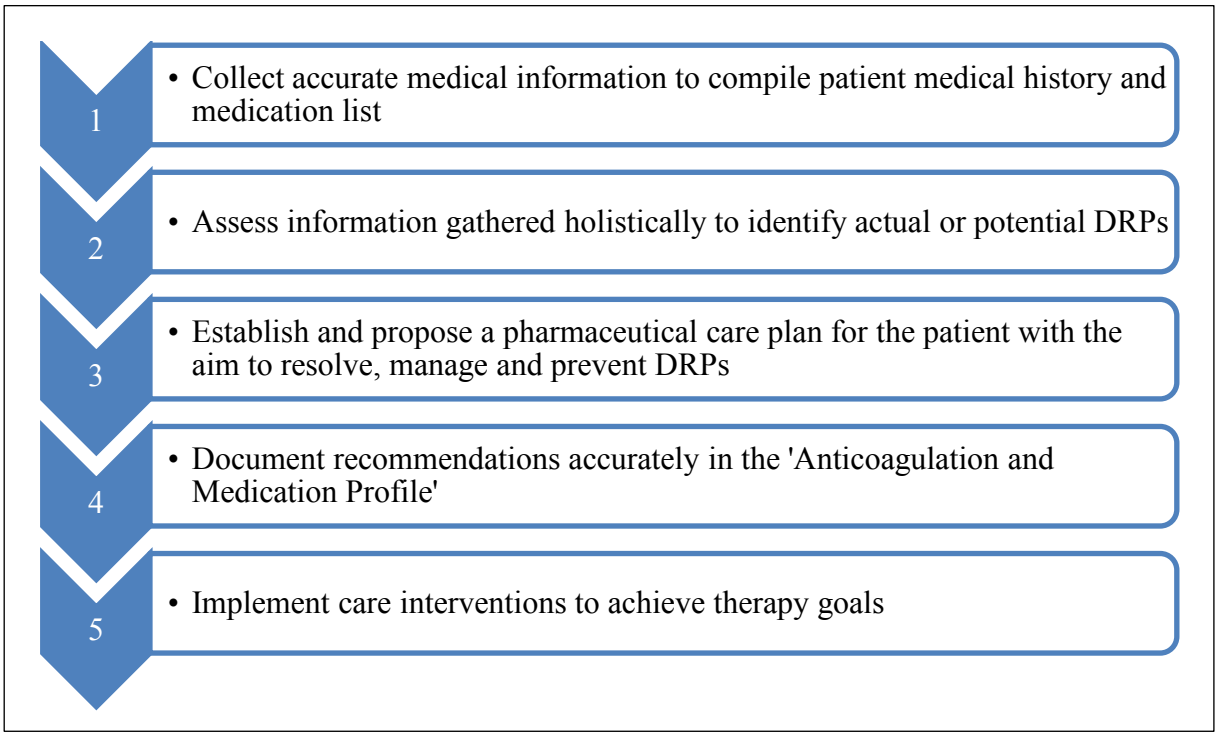


Figure 2.3: Medication reconciliation procedure

Data was compiled in the developed 'Anticoagulation and Medication Profile' (Appendix 2). Patients were asked to provide the pharmacist researcher with medical documents such as outpatient medication records, hospital discharge letters, repeat prescriptions and Schedule V documents, which were consulted to obtain additional data regarding the medical history. Data collected was verified between the different sources. Clinical judgement was used throughout the procedure to determine if sources available were accurate to compile the patient medication profile. The patient was asked to explain the administration routine of each medication and was specifically asked about use of over-the-counter medications (OTCs), vitamins or herbal supplements.

For each patient, the 'Medication profile' in section D of the 'Anticoagulation and Medication Profile' was completed to include a comprehensive summary of all chronic medications. Details listed in the profile included dose, formulation, dosage regimen

and administration instructions. The following points were followed while completing the medication profile in section D:

i. The medication list was inputted in alphabetical order according to the generic name and well-known brand names were listed in the appropriate field.
ii. The dose listed in the profile was the amount of active ingredient present in each unit of medicine, appropriate units were written and use of decimal places was avoided.
iii. The dosage regimen was documented by listing the number of tablets or units to be taken at a specified time (breakfast, lunch, dinner or bedtime).
iv. In the last column 'Counselling Points and Administration Instructions', notes related to medication use were included, for example how medications must be administered, foods or medications to avoid, notes on special storage conditions and common side-effects of each medication. The British National Formulary (BNF) (2016) was used as a reference when writing these recommendations.

Following compilation of the medication profile, the medication list was discussed with the patient. The pharmacist researcher explained the reason for the medications prescribed and provided verbal advice.

2.14.4 Development of pharmaceutical care plan

The medical history and medication use compiled in the 'Anticoagulation and Medication Profile' (Appendix 2) were evaluated and comprehensively reviewed by the pharmacist researcher to identify, solve and prevent DRPs. All medications were assessed to identify side-effects, contraindications, DDIs and need for routine monitoring whilst confirming that the patient understands the treatment rationale and is

adhering to treatment. A pharmaceutical care plan was developed, where problems associated with medications were identified and clinical interventions recommended to optimise medication use and treatment outcomes.

2.14.4.1 Classification of drug-related problems

As a guideline to facilitate identification of DRPs and assist in accurate classification, the structured flowchart based on the concepts presented in the DOCUMENT classification proposed by Williams et al (2012) was followed (Figure 2.4). The categories and subcategories in the DOCUMENT classification are defined in Appendix 6. Professional clinical judgement was used by the pharmacist researcher to select the most appropriate category, particularly in cases where it was difficult to classify a DRP due to overlap or unclear areas.

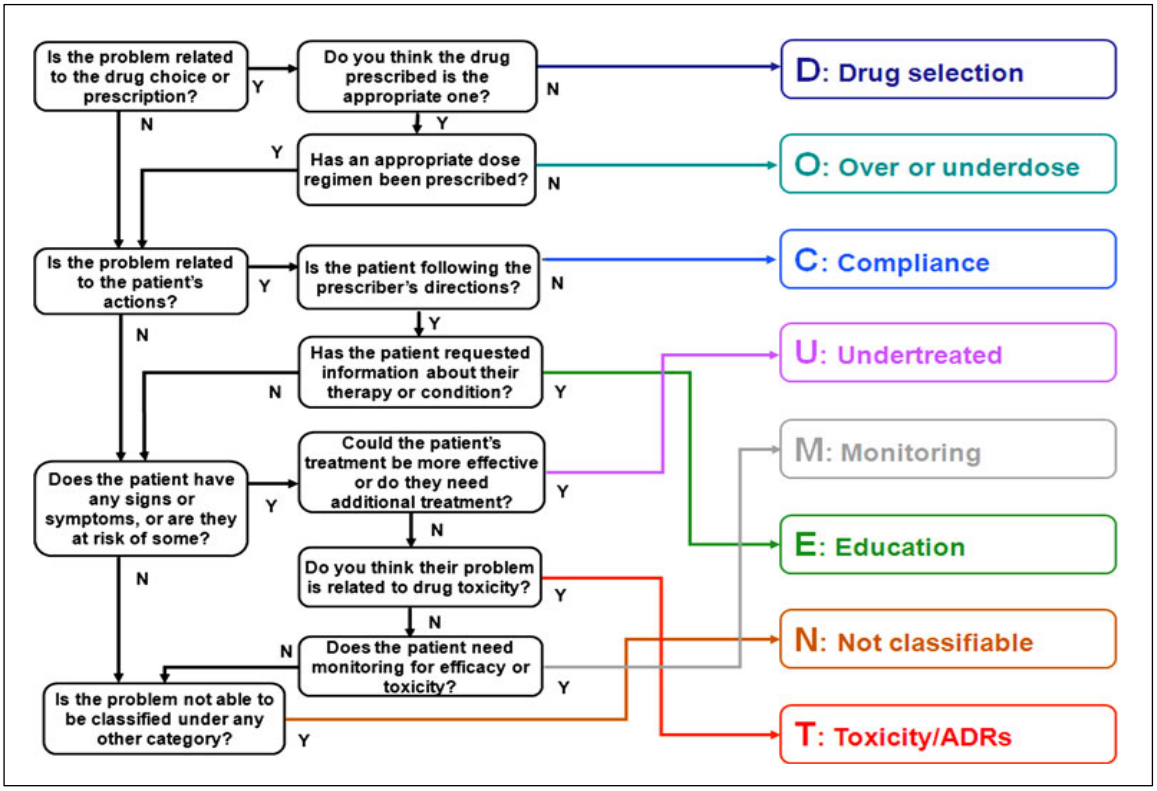


Figure 2.4: Flowchart to facilitate classification of drug-related problems according to DOCUMENT

Reproduced from: Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: A system for classifying drug-related problems in community pharmacy. Int J Clin Pharm 2012;34 (1):43-52.

Eleven new subcategories were developed under the 'Other' subcategory in five of the DOCUMENT categories to enable classification of DRPs that could not be classified in the defined categories (Table 2.7).

Table 2.7: 'Other' subcategories added to DOCUMENT classification

DRP category	New subcategories
Drug selection	Need for treatment
	Duration of treatment
Compliance	Suboptimal timing of medication administration
	Difficulty in changing warfarin dose
	Patient non-compliant with INR tests
Monitoring	No INR requested after administration of interacting medication
Education and information	Patient education to address gaps identified from the knowledge test
Not classifiable	Smoking cessation
	Alcohol binging
	Obesity
	Confirm INR target range

Following identification and classification of DRPs, action to be taken was planned and a clinical intervention to solve each DRP was recommended. The researcher's clinical skills were used to provide timely interventions classified according to the 'Recommendations' section in the DOCUMENT classification system which consists of five categories and nineteen subcategories (Williams et al, 2012). The 'Refer to prescriber' recommendation was further developed by dividing it into seven new sub-categories to allow for better explanation of the pharmacist researcher's recommendations (Table 2.8).

Table 2.8: Recommendations classification

Category	Subcategory
Change in therapy	Dose increase
	Dose decrease
	Drug change
	Drug formulation change
	Drug brand change
	Prescription not dispensed
Referral required	Refer to prescriber • Change dosage • Change drug • Change instruction of use • Close assessment of the risk benefit ratio of the treatment • Confirm dosage • Start new drug • Stop drug
	Refer to hospital
	Refer for medication review
	Other referral required
Provision of information	Education or counselling session
	Written summary of medications
	Recommend dose administration aid (DAA)
	Other written information
Monitoring	Laboratory e.g. general blood tests
	Non-Laboratory e.g. blood pressure testing, POC glucose testing
Other	Other recommendations that cannot be classified under another subcategory

Adapted from: Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: A system for classifying drug-related problems in community pharmacy. Int J Clin Pharm 2012;34 (1):43-52.

For each patient, an individualised pharmaceutical care plan was developed, consisting of medication management strategies and recommendations for the identified DRPs according to the patient's treatment goals. All recommendations were documented in Section E of the 'Anticoagulation and Medication Profile' and discussed with the patient. The health professional responsible to intervene to address the identified DRP and implement the suggested clinical intervention was selected in the 'Consideration by' field.

Communication and explanation of identified DRPs to the patient was undertaken in a sensitive manner, where essential information was provided without alarming the patient and respecting the discretion of the physician. Issues that could be addressed at clinical pharmacist level, such as issues of non-adherence, concerns about side-effects and need for education and information were dealt with during the MUR session, with provision of pharmaceutical advice and counselling by the researcher. Recommendations which required actions by the patient to change practices to improve treatment management and resolve the identified DRPs were explained to the patient. The pharmacist researcher intervened according clinical and interventions which required physician intervention were referred accordingly by advising the patient to contact the family physician to discuss the recommendations presented in the pharmaceutical care plan. Patients requiring adherence aids or who had issues related to the dispensing process were referred to the community pharmacist.

At the end of the session, the pharmacist researcher summarised the important points discussed and the patient was allowed to ask questions. The patient was advised that a follow-up session will be performed after two months and was encouraged to seek

assistance from the community pharmacist for ongoing support. The 'Anticoagulation and Medication Profile' (Appendix 2) with compiled data was given to the patient to serve as a medical record to facilitate communication between different health professionals and to help the patient understand the treatment. The patient was encouraged to keep the profile updated. After each MUR session, data collected was transferred to Microsoft® Excel® 2010 and a computerised patient record was developed for each patient to record the medication regimen, INR target range, INR result obtained with the CoaguChek®XS device , past INR results, list of DRPs and recommended clinical interventions.

2.15 Follow-up pharmacist-led consultation

Two months after the MUR session the patient was contacted again for a follow-up appointment. The patient was asked to bring the 'Anticoagulation and Medication Profile' (Appendix 2) compiled during the MUR session, recent health-related documents, Schedule V card and yellow anticoagulation booklet. During part one of the follow-up session, the post-intervention questionnaire (Appendix 1) was completed to assess changes in patient knowledge on anticoagulation, adherence to warfarin and perception regarding the MUR service. Any educational gaps were re-emphasised. During the second part, medication reconciliation was carried out to assess changes or improvements from the MUR session. Patient documentation was reviewed to identify changes in treatment.

The degree of acceptance of the pharmacist researcher's recommendations was determined by identifying the number of DRPs for which action was taken to solve or monitor the problem. The outcomes of each recommendation were classified as;

'improved compliance', 'improved knowledge', 'monitoring carried out', 'change in treatment', 'advice taken into consideration' and 'use of dose administration aids'. DRPs which were not solved since no action or change was implemented were also documented. DRPs which were not addressed by the physician were classified as either 'discussed with physician recommendation not accepted' or 'not discussed with physician'. The impact of the developed individualised pharmaceutical care plan was determined according to the number of recommendations that were acted upon by the patient and/or addressed by the physician following the MUR session.

The research methodology was assessed in a pilot study on ten patients. The MUR and follow-up session procedure were tested for feasibility, practicality and applicability. The ten patients were recruited by convenience sampling. No major difficulties were encountered during the pilot study. The study design and research tools developed were established to be satisfactory and could be used for the main study. The same methodology applied in the pilot study was used to recruit and assess another ninety patients. Patient recruitment and data collection took place over an eight-month period, from April to December 2016.

2.16 Data analysis

Data collected was statistically analysed using IBM SPSS Statistics 24. Descriptive statistics were used to describe the main features of the study population and to assess the frequencies for all questions. Categorical variables were described by frequencies and percentages, while continuous variables were described by mean and standard deviation (SD). From the data collected, the level of knowledge about anticoagulation,

adherence to treatment, patient perception on the current anticoagulation management service and the proposed pharmacist-led anticoagulation clinic were summarised.

2.16.1 Warfarin knowledge score

Two different coding methods were used to determine the level of anticoagulation knowledge. In the first method, each patient was awarded a score for the responses given to questions 2 to 13 in Section 1 'Warfarin knowledge test'. A dichotomous scale was used, with correct responses scoring 1 point, while 0 points were awarded for missing or wrong answers. The maximum total score was twelve and a score of nine correct answers (75%) was defined as the pass score indicating an adequate level of knowledge (Baker et al, 2011; Collins et al, 2014; Shrestha et al, 2015). Need for an educational intervention was identified for patients who did not obtain a pass score which was considered as a DRP. In the second method, the actual responses provided by the patient were coded to allow analysis of the type of responses given and how responses changed post-intervention. Patient responses identified educational gaps and allowed targeted educational sessions.

2.16.2 Adherence score

An adherence score was developed as a tool to objectively measure and monitor how factors that affect INR control are managed. The adherence score expands the focus from assessing the number of missed warfarin doses to assess adherence to other factors that can affect the action of warfarin (Table 2.9). One point was awarded to each factor that may negatively affect INR control, with a maximum total score of ten. The higher the score, the poorer the adherence. An analysis on how the adherence score changed post-intervention was carried out to assess the impact of pharmacist intervention.

Table 2.9: Adherence assessment tool

Factor	**Score**	**Awarded score**
Patient taking wrong dose	1	
Patient missed one dose Patient missed two doses Patient missed three doses or more	1 2 3	
Patient took an extra dose Patient took 2 extra doses Patient took 3 or more extra doses or more	1 2 3	
Patient did not attend for INR test	1	
Variable consumption of Vitamin K-containing food	1	
Variable alcohol consumption	1	
	Total score	

2.16.3 Assessing clinical significance of identified drug related problems

The pharmacist researcher assigned the perceived significance of each clinical recommendation provided according to the six levels of significance namely; a) intervention is detrimental to patient health, b) intervention is of no significance to patient care, c) intervention is significant but does not result in an improvement in patient care, d) intervention is significant and results in an improvement in patient care, e) intervention is very significant and prevents major organ damage or an adverse reaction of similar importance, and f) intervention is potentially life-saving (Hulls and Emmerton, 1996; Williams, 2013).

2.16.4 Analysis of pharmacist intervention

Data collected pre-intervention during the MUR session was compared to data collected post-intervention during the follow-up session. The impact of the pharmacist intervention was assessed by determining improvements, if any, in anticoagulation knowledge score, warfarin adherence, and patient perception of pharmacist competencies. All compiled patient medical data was assessed to determine the frequency and type of prescribed medication, comorbidities and DDIs. The impact of the pharmacist intervention was evaluated by assessing the nature and frequency of the detected DRPs, clinical significance, physician, patient or community pharmacist acceptance of the recommendations and the number of implemented recommendations. The rate of acceptance was determined using percentages and proportions.

2.16.5 Assessment of time in therapeutic range

Time in therapeutic range (TTR) is a determinant of the quality of anticoagulation treatment and its therapeutic effectiveness (Ansell et al, 2001). The mean percentage time patient spent above, below and within the optimal therapeutic range in the two months before and after the pharmacist intervention was calculated to assess INR control. The Rosendaal linear interpolation method was used to estimate the TTR of each patient. It was assumed that the actual change between two consecutive INR test values varies linearly (Rosendaal et al, 1993).

The days between each two INR test appointments, in the two months pre- and post-intervention, were counted and divided in halves; the first half was allocated to the first INR result while the second half was allocated to the consecutive INR result. Subsequently, the number of days calculated were classified as below therapeutic range

(BTR), within therapeutic range (WTR) or above therapeutic range (ATR) and summed up accordingly. The percentage duration spent BTR, WTR and ATR was calculated for both pre- and post-intervention INR results using the equation:

$$\frac{\text{Number of days spent BTR or WTR or ATR}}{\text{Total number of days}} \times 100$$

2.17 Statistical analysis

The Shapiro-Wilk test, a test to determine data normality, was used to assess the distribution of the number of DRPs and pre- and post-intervention knowledge score. The null hypothesis specified that the distribution was normal and was accepted if the p-value exceeds the 0.05 level of significance, while the alternative hypothesis specified that the distribution was skewed and was accepted if the p-value was less than the 0.05 criterion. The Shapiro-Wilk p-values were all less than the 0.05 criterion indicating that the number of DRPs, pre- and post-intervention knowledge score distribution were skewed, hence non-parametric statistical tests were used for analysis.

The Wilcoxon Signed Rank Test was used to compare mean scores pre- and post-pharmacist intervention for the knowledge score, adherence score, Likert scale ratings and TTR. The null hypothesis specified that mean score post-intervention was comparable to mean score pre-intervention (pharmacist intervention not effective) and was accepted if the p-value exceeds the 0.05 criterion. The alternative hypothesis specified that the mean score post-intervention was significantly higher than the mean score pre-intervention (pharmacist intervention is effective) and was accepted if the p-value was less than the 0.05 criterion.

The chi-square Test was used to assess the association between two categorical variables. The null hypothesis specified that there is no association between the two categorical variables and is accepted if the p-value exceeds the 0.05 level of significance, while the alternative hypothesis specified that there is a significant association between the two categorical variables and is accepted if the p-value is less than the 0.05 criterion.

The Spearman Correlation Coefficient measures the strength of the relationship between two continuous variables having a metric scale which are not normally distributed. The Spearman Correlation Test is a non-parametric alternative to the Pearson Correlation Test. It ranges from -1 to 1, where a negative correlation coefficient indicates a negative relationship, a positive correlation coefficient indicates a positive relationship and a correlation close to zero indicates no relationship. The null hypothesis specified that there was no relationship between the variables and was accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specified that there was a significant relationship between the two variables and was accepted if the p-value was less than 0.05 criterion. The Spearman Correlation Test was used to determine the association between the number of DRPs and the number of medications, number of conditions and age, and to determine the relationship between knowledge score and age, warfarin-related DRPs and knowledge score and patient perception on their level of knowledge and actual knowledge score.

The 'Difference between two proportions test'[18] was used to assess if the percentage of accepted recommendations significantly exceeded the percentage of rejected

[18]Social Science Statistics. Z-Score calculator for 2 population proportions [Internet]. 2017 [cited 2017 May 05]; Available from: http://www.socscistatistics.com/tests/ztest/Default2.aspx

recommendations. The null hypothesis states that there is no difference between the percentage of accepted or rejected recommendations and is accepted if the p-value exceeds the 0.05 level of significance, while the alternative hypothesis specified that there is a significant difference between the percentage of accepted or rejected recommendations and is accepted if the p-value is less than the 0.05 criterion.

The Kruskal-Wallis test was used to assess whether a statistically significant difference exists between two or more groups. The test was used to compare the mean knowledge score between several independent groups clustered either by gender, duration of treatment or age. The null hypothesis specified that mean knowledge scores vary marginally between the groups and was accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specified that mean knowledge scores vary significantly between groups and was accepted if the p-value is less than the 0.05 criterion. This test was used to assess the relationship between knowledge score and adherence to warfarin.

Chapter 3

Results

3.1 Study population

The total study population consisted of 100 patients on warfarin who attended for the MUR session and medication reconciliation was performed (t=0). In the follow-up session (t=1), one patient withdrew from the study, hence medication reconciliation was performed for 99 patients. Medication reconciliation identified two patients who stopped taking warfarin since they were switched to a NOAC, hence for comparison of the warfarin knowledge score, adherence score and INR control between t=0 and t=1, 97 patients were considered.

3.2 Patient demographics and lifestyle factors

Hundred patients were recruited (56 male, 44 female; mean age 70.48 ±10.30, range 33-89 years). Thirty-four patients were in the 70-79 years age category (Figure 3.1).

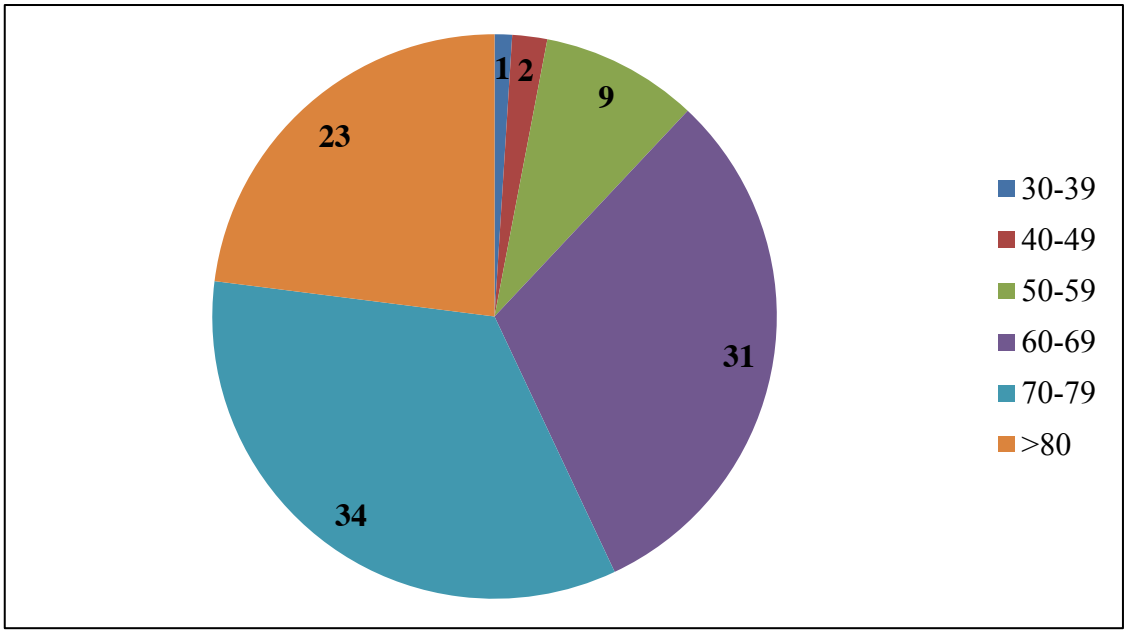


Figure 3.1: Age distribution of the study population (N=100)

Seventy-six patients had only primary education, followed by 22 patients who had secondary education and 2 patients who had tertiary education.

Of the 100 patients, 67 patients never smoked, 22 patients were past smokers and 11 patients were current smokers. Forty-eight patients do not consume any alcohol, 32 patients consume 1 unit daily, 13 patients consume variable amounts of alcohol but do not exceed 4 units daily and 4 patients binge drink.

3.3 Treatment with warfarin

The indication for warfarin, duration of treatment, INR ranges and POCT INR results are reported.

3.3.1 Indications for warfarin

Seventy-one patients were prescribed warfarin for prophylaxis or treatment of thromboembolic complications associated with atrial fibrillation (AF) (Table 3.1).

Table 3.1: Warfarin indication (N=100)

Warfarin indication	Number of patients
Atrial Fibrillation	**71**
Heart Valve Replacement	13
Deep Vein Thrombosis	10
Ischaemic Heart Disease	3
Pulmonary Embolism	3

3.3.2 Duration of warfarin treatment

Fifty-four patients had been taking warfarin for more than 5 years (Table 3.2).

Table 3.2: Duration of warfarin treatment (N=100)

Duration of warfarin treatment	Number of patients
3-6 months	12
>6 months-1 year	7
>1 year-5 years	27
> 5 years	**54**

3.3.3 Therapeutic INR range

Sixty-two patients had a target therapeutic INR range of 2.0 to 3.0 (Table 3.3).

Table 3.3: INR range (N=100)

INR range	Number of patients
2.0-3.0	**62**
1.8-3.0	15
2.0-2.5	10
2.5-3.5	4
3.0-3.5	2
1.5-2.5	2
1.8-2.0	2
1.8-2.2	1
1.8-2.4	1
2.0-3.2	1

3.3.4 Point-of-care INR results

Of the 100 INR tests performed, 60 patients had an INR value within their target therapeutic range. Twenty-eight of the 40 patients who obtained an out-of-range INR result were referred for an INR test at the government health centre, while the remaining 12 patients were not referred since they had a dose change five days prior to the POC test or had a scheduled INR test in the following three days (Figure 3.2).

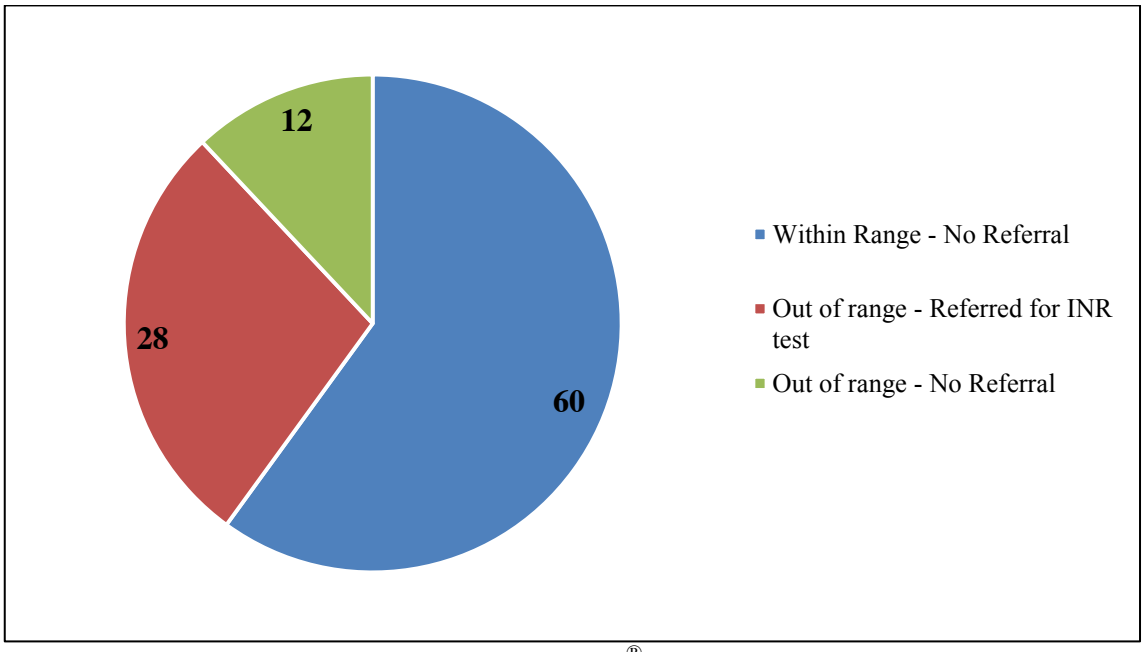


Figure 3.2: INR results obtained by CoaguChek®XS and action taken (N=100)

The mean INR result for the study population was 2.48 (±0.72, range 1.0-5.6). Fifty-eight patients obtained a result between 2.0 and 3.0 (Figure 3.3). The patient who obtained an INR result of 1.0 was non-compliant to warfarin and had skipped three or more warfarin doses, while the patient who obtained an INR result of 5.6 was not attending for INR testing, with the last INR test at the government health centre performed more than three months prior to the MUR session.

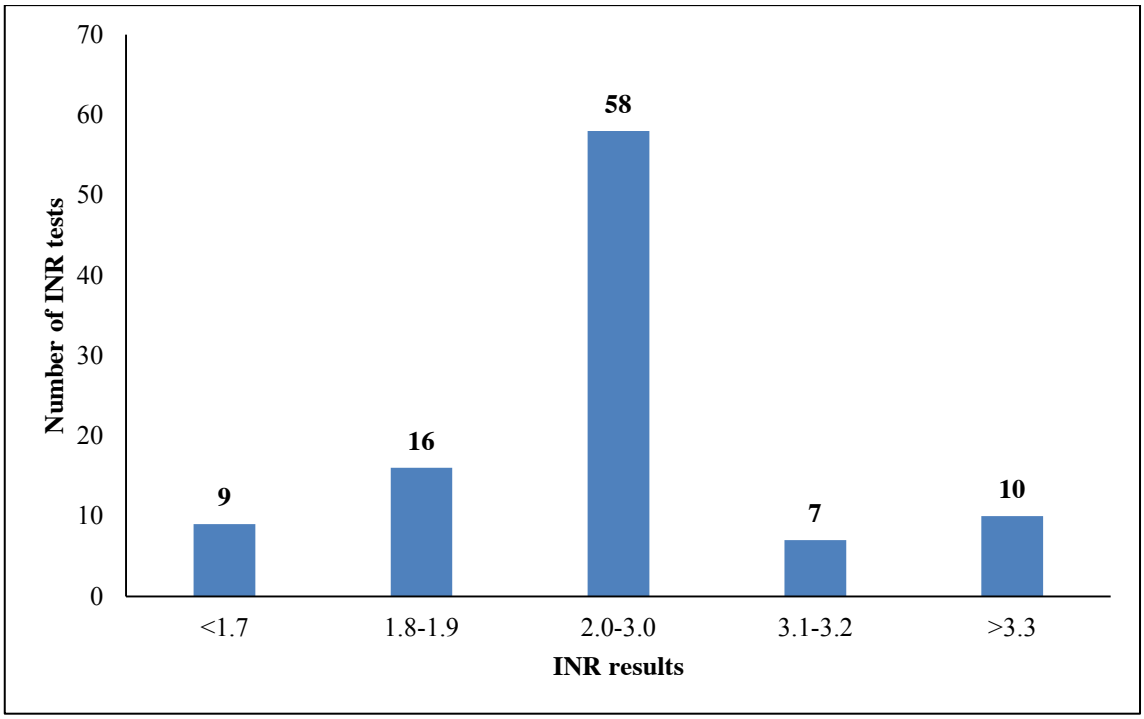


Figure 3.3: Distribution of point-of-care INR results (N=100)

3.4 Comorbidities

The patients suffered from a total of 328 medical conditions, including the condition for which warfarin was indicated, with a mean of 3.28 conditions per patient (±1.18, range 1-8 conditions). Aside from the condition for which warfarin is indicated, 5 patients had no other comorbidity, 16 had one comorbidity, 44 had two comorbidities, 22 had three comorbidities and 13 had four or more comorbidities. Sixty-seven patients suffered from hypertension (29.4%) (Table 3.4).

Table 3.4: Comorbidities (N=228)

Comorbidity	Frequency	Percentage (%)
Hypertension	**67**	**29.4**
Diabetes mellitus	22	9.7
Coronary Artery Disease	19	7.0
Hypercholesterolaemia	15	6.6
Hypothyroidism	14	6.1
Anxiety/Psychoses	13	5.7
Congestive Heart Failure	13	5.7
Depression	10	4.4
Arthritis	9	3.9
Asthma	7	3.1
Gastro-oesophageal reflux disease	6	2.6
Prostate disease	6	2.6
Others[a]	18	7.9

[a]Others include gout, glaucoma, anaemia, diverticulosis, osteoporosis, Bechet disease, C+S protein deficiency, chronic constipation, Crohn's disease, End stage renal failure, kidney transplant, pancreatic exocrine insufficiency, past breast cancer, sleep apnoea, sodium deficiency

3.5 Warfarin knowledge test

The warfarin knowledge test was performed pre- and post-pharmacist intervention in 97 patients.

3.5.1 Pre-intervention warfarin knowledge score

A mean score of 7.42 out of 12 (range 3-12) was observed in the warfarin knowledge test pre-intervention, with 25 patients obtaining a pass score of 9 or more out of 12 and only two patients answered all 12 questions correctly (Figure 3.4).

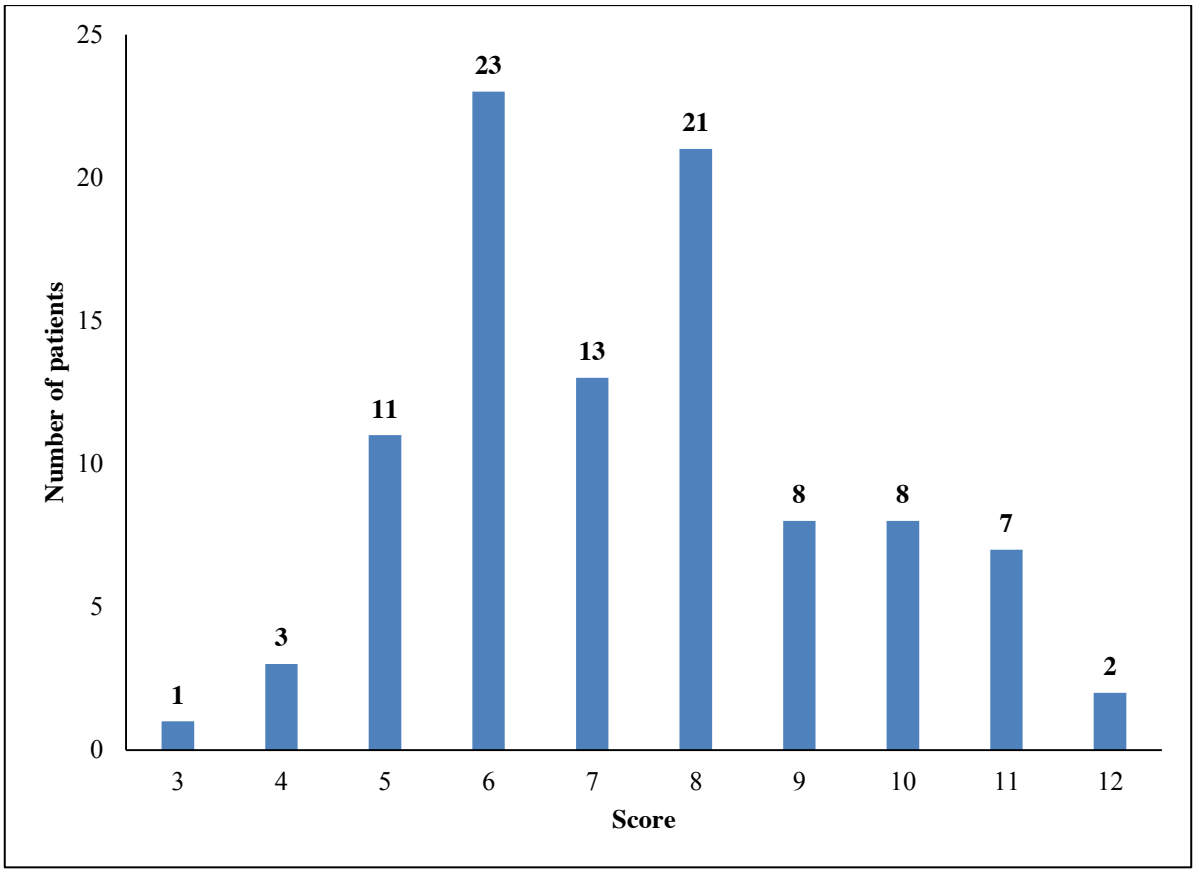


Figure 3.4: Scores obtained in warfarin knowledge test pre-intervention (n=97)

A statistically significant difference ($p<0.05$) in the mean knowledge score between males and females was observed. Males obtained a mean score of 7.80 (±2.084) while females obtained a mean score of 7.02 (± 1.861). A statistically significant difference in mean knowledge score between the different age groups was observed ($p<0.05$). The ≤60 year age group obtained the highest mean score (mean 8.30, ±2.136) while the ≥81 years age group obtained the lowest mean score (mean 6.50, ±1.789) (Table 3.5).

Table 3.5: Relationship between warfarin knowledge score and age (n=97)

Age group (years)	Number of patients	Mean knowledge score	SD	p-value
≤60	**13**	**8.31**	**2.136**	0.001
61-70	35	8.20	1.779	
71-80	33	6.70	1.830	
≥81	16	6.50	1.789	

$X^2(3)= 16.186$, p=0.001

A decline in mean score was observed with increasing age. A statistically significant inverse relationship between patient age and level of anticoagulation knowledge was observed (Spearman Correlation Coefficient -0.375, $p<0.05$).

No relationship between the level of anticoagulation knowledge and the duration of anticoagulation was observed since the difference in the mean knowledge score was not significant and varied marginally between the treatment duration groups ($p>0.05$) (Table 3.6).

Table 3.6: Relationship between knowledge score and duration of anticoagulation (n=97)

Duration of treatment	Number of patients	Mean	SD	p-value
3-6 months	10	7.3	2.21	0.739
>6 months-1 year	7	6.57	1.512	
>1-5 years	26	7.50	1.900	
>5 years	**54**	**7.52**	**2.063**	

$X^2(3)= 1.259$, p=0.739

3.5.2 Post-intervention warfarin knowledge score

A mean score of 9.63 out of 12 (±1.764, range 6-12) was obtained in the post-intervention knowledge test. Sixty-six patients obtained a pass score of 9 out of 12 and 20 patients answered all 12 questions correctly post-intervention (Figure 3.5).

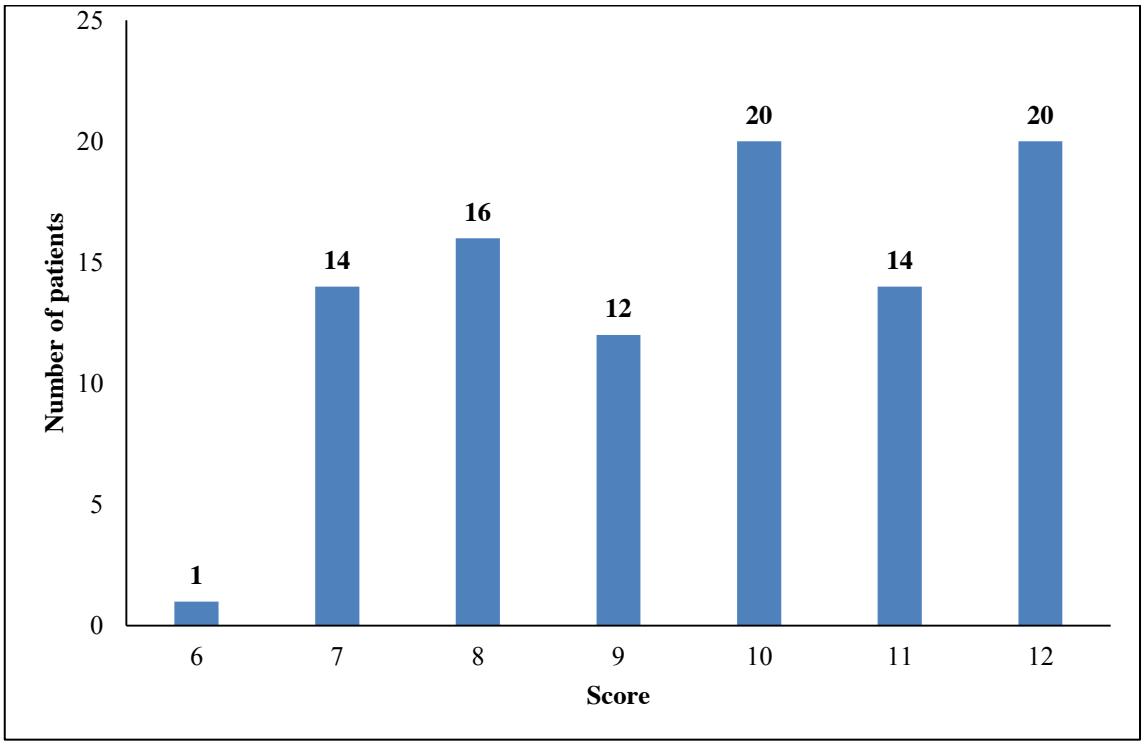
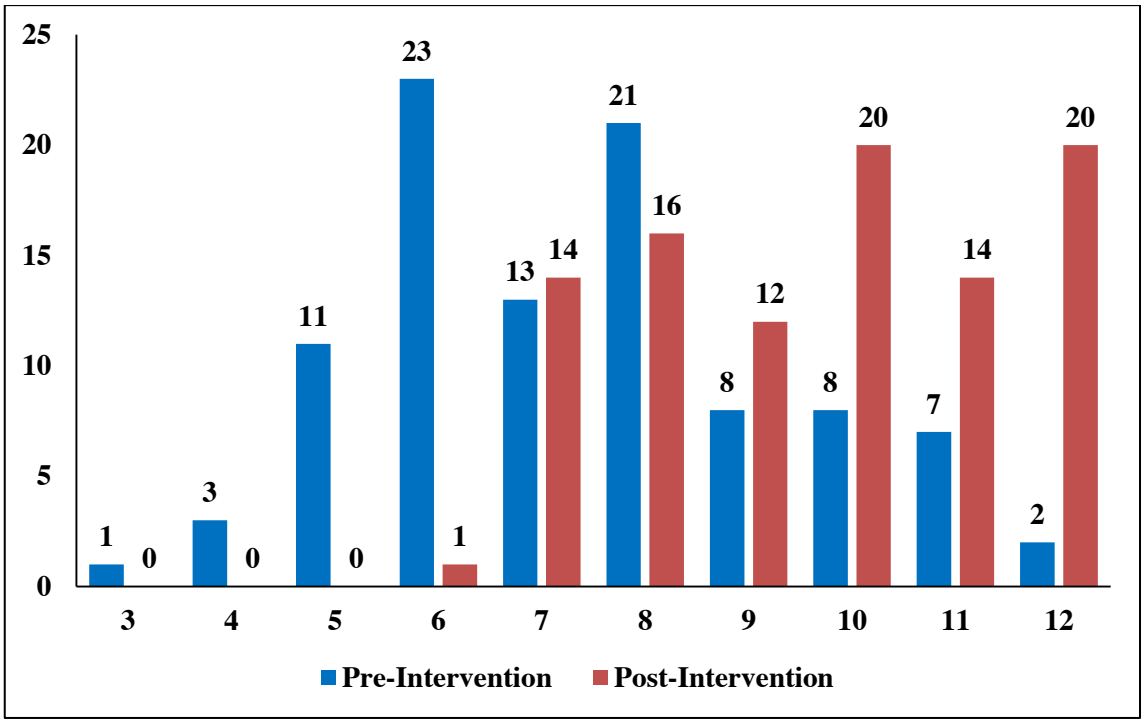


Figure 3.5: Scores obtained in warfarin knowledge test post-intervention (n=97)

3.5.3 Improvement in knowledge test post-intervention

Post-intervention, 88 patients improved their knowledge score, no change in score was observed in 8 patients, while 1 patient obtained an inferior score. The mean knowledge score post-intervention (mean 9.63 ±1.764) exceeds the mean knowledge score pre-intervention by 2.21 (mean 7.42 ±1.989). The Wilcoxon Signed Ranks Test showed that the improvement in knowledge score post-intervention was significant ($p<0.05$) (Figure 3.6).



z-score:-8.163, p-value<0.001

Figure 3.6: Comparison of scores obtained in warfarin knowledge test pre- and post-intervention (n=97)

A statistically significant negative relationship between age and improvement in knowledge score was observed, indicating that as age increases improvement in knowledge score post-intervention is expected to decrease (Spearman Correlation coefficient -0.220, $p<0.05$). The mean improvement in knowledge score in females exceeded the mean improvement in score for males, but the relationship was not statistically significant ($p>0.05$).

In the pre-intervention knowledge test, the patients gave a correct response to questions concerning side-effects (n=92), warfarin administration (n=90), warfarin indication (n=87) and the need to always inform health professionals of warfarin administered (n=75). The knowledge deficiencies observed, included the possible consequences of under (n=45) and over (n=31) anticoagulation, management of missed doses (n=40) and warfarin interactions (n=26). The chi-square test established that the number of patients

providing a correct answer increased significantly in 10 out of the 12 questions ($p<0.05$), except for question 5 and 6 ($p>0.05$) (Table 3.7).

Table 3.7: Improvement in the number of correct responses post-intervention (n=97)

Question		Number of correct answers		Chi-square value	p-value
		Pre-intervention	Post-intervention		
2	Warfarin indication	87	97	10.543	0.001*
3	Indication for INR testing	80	94	10.926	0.001*
4	Risks of high INR results	31	47	5.489	0.019*
5	Risks of low INR results	45	59	2.977	0.084
6	Main side-effect of warfarin	92	96	2.752	0.097
7	Importance of reminding health professional on warfarin intake	75	94	16.576	0.000*
8	Distinguish between different strengths of warfarin	91	97	6.191	0.013*
9	Warfarin interactions	26	68	36.406	0.000*
10	Warfarin-food interactions	35	57	10.006	0.002*
11	Optimal time for warfarin administration	90	96	4.694	0.030*
12	Managing missed warfarin dose	57	90	30.578	0.000*
13	Warfarin- drug interactions	32	49	6.125	0.013*

*$p<0.05$: Statistically significant

3.6 Adherence to warfarin

Pre-intervention, 25 patients missed at least one warfarin dose in the two weeks prior to the MUR session, of which 2 confirmed missing three or more doses. Three patients took a double warfarin dose in the same period and four patients were taking a different warfarin dose to the one prescribed. Sixteen out of the 25 patients who missed at least one dose were male with mean age of 73.24 years. The mean knowledge test score of patients who were adherent to treatment (7.63) exceeded the mean knowledge test score of non-adherent patients (6.80), however the difference in mean score was not statistically significant ($p>0.05$).

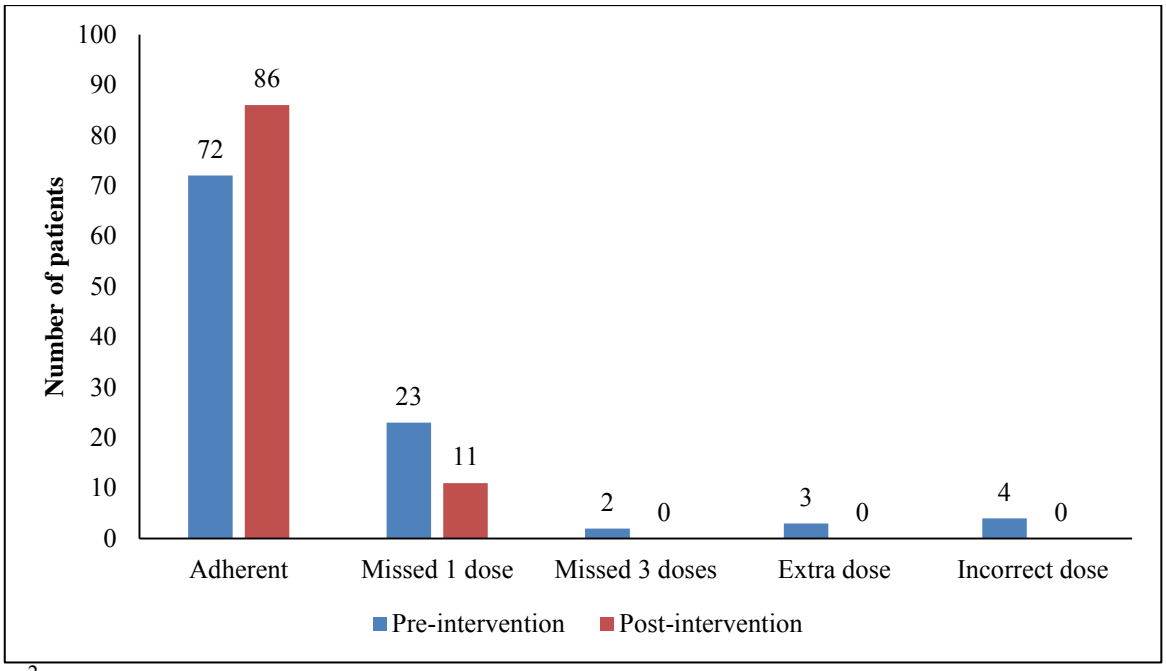
A statistically significant ($p<0.05$) decrease from 25 to 11 patients who skipped a warfarin dose in the fortnight prior to the post-intervention follow-up session was observed (Table 3.8).

Table 3.8: Improvement in warfarin adherence post-intervention (n=97)

Adherence			**Pre-intervention**	**Post-intervention**
Did you skip a warfarin dose?	Yes	Number of patients	25	11
		%	25.8	11.3
	No	Number of patients	72	86
		%	74.2	88.7

$X^2(1) = 6.685$, $p = 0.010$

Post-intervention, none of the patients missed more than one dose, took an extra dose or were administering an incorrect dose (Figure 3.7).



$X^2(1) = 6.685$, $p = 0.010$

Figure 3.7: Comparison of warfarin adherence pre- and post-intervention (n=97)

3.6.1 Warfarin dosing

During the MUR session, 75 patients were on a warfarin dose less than 5mg. The mean warfarin dose was 4.1mg (range 0.5-11mg), with 59 patients on the same daily warfarin dose and 38 patients on alternate-day dosing. During the follow-up session, 70 patients were on a warfarin dose less than 5mg. The mean warfarin dose was 4.1mg (range 1-11mg), with 65 patients on the same daily warfarin dose and 32 patients on alternate-day dosing.

During the MUR session, when patients were asked to indicate the current warfarin dose, 57 patients indicated the dose by specifying the colour of the tablets, 37 specified the actual dose in milligrams and 3 were not aware of the dose they were taking since the medication is prepared by a relative/carer. When the dose specified by the patient

was compared with the dose written on the anticoagulation booklet 4 patients were identified as administering a wrong dose to the one prescribed. In 17 patients medications were prepared by a relative/carer.

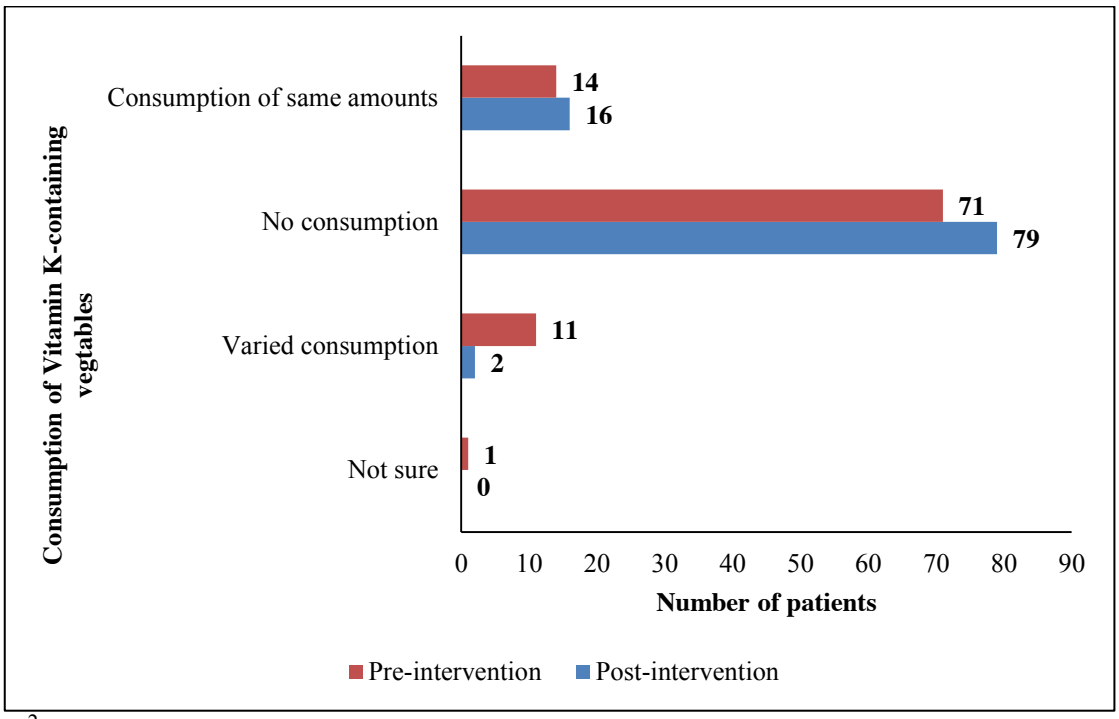
In the follow-up session, 61 patients stated their dose using tablet colour and 36 indicated the dose by specifying the actual dose in milligrams. All patients were administering a correct dose and were aware of the dose that should be taken. The number of patients who prepared their medication decreased by 1 during the post-intervention session since 1 patient was having the medication prepared by the community pharmacist. Patients felt more comfortable to modify their warfarin dose post-intervention with a significant decrease from 31 to 15 patients stating finding difficulty in adjusting the warfarin dose ($X^2(1) = 7.295$, $p<0.05$).

3.6.2 Compliance to INR testing

During the MUR session, 11 patients confirmed that they had missed an INR testing appointment in the two months prior to the MUR session. Reasons for missing INR testing appointments included forgetting the day that the test is due (n=5), being unwell on the day of the test (n=3) and due to transport problems (n=2). Ten patients postponed their missed INR testing appointment while 1 patient did not attend for INR testing in the three months prior to the session. A statistical significant ($p<0.05$) improvement in compliance to INR testing was observed, with only 1 patient missed an INR test appointment in the two months prior to the follow-up session.

3.6.3 Warfarin-diet interactions

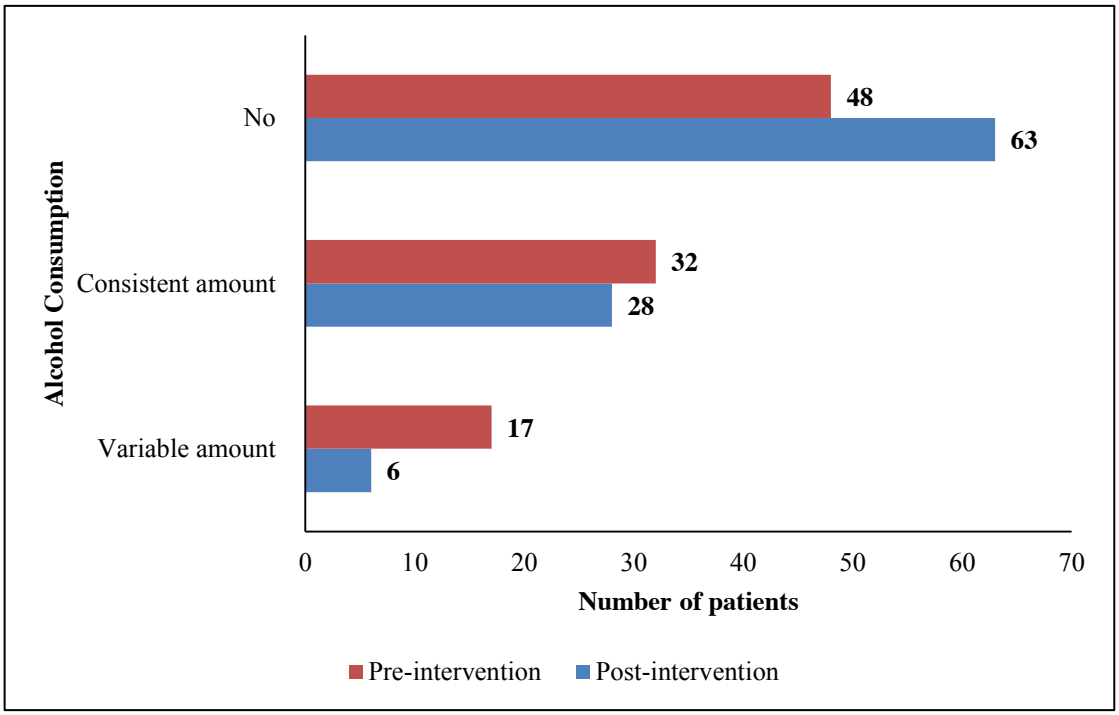
In the MUR session, 11 patients stated that the daily intake of Vitamin K-containing vegetables varied, while 71 patients stated that no Vitamin K-containing vegetables are consumed. Consistency in consumption of Vitamin K-containing vegetables improved post-intervention although not significantly ($p>0.05$) (Figure 3.8).



$X^2(1) = 7.791$, $p = 0.051$

Figure 3.8: Consumption of Vitamin K-containing vegetables pre- and post-intervention (n=97)

The number of patients who did not consume any alcohol increased significantly from 48 patients pre-intervention to 63 patients post-intervention ($p<0.05$). The number of patients consuming variable amounts of alcohol decreased from 17 patients pre-intervention to 6 patients post-intervention ($p>0.05$) (Figure 3.9).

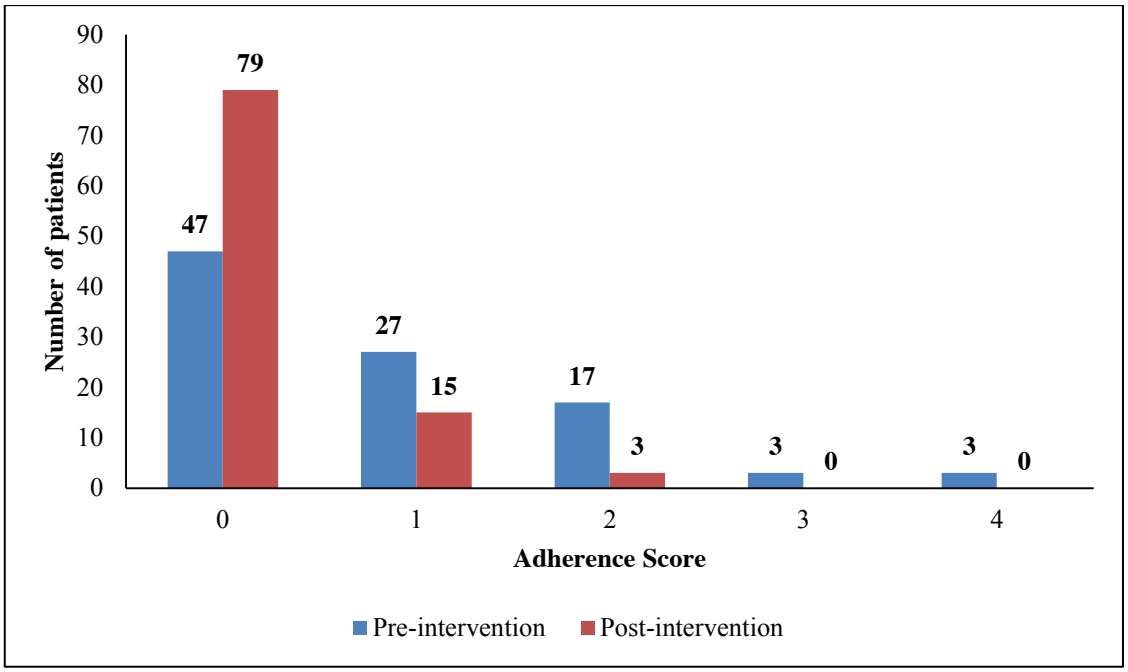


$X^2(1) = 7.555$, $p = 0.023$

Figure 3.9: Alcohol consumption pre- and post-intervention (n=97)

3.6.4 Adherence score

A mean adherence score of 0.85 per patient (±1.02, range 0-4) was obtained in the adherence assessment tool pre-intervention. High scores demonstrate low patient adherence. A significant decrease in the mean adherence score was observed post-intervention (mean 0.22 per patient, ±0.48, range 0-2) ($p<0.05$). The number of patients scoring 0, increased significantly ($p<0.05$) from 47 to 79 patients post-intervention showing an improvement in patient adherence and understanding (Figure 3.10).



z-score -5.640, p<0.001

Figure 3.10: Pre- and post-intervention adherence score (n=97)

3.7 Current anticoagulation management system

Out of the 100 patients recruited, 52 tested the INR by venepuncture and 48 tested INR with a POCT device using the finger-prick method to obtain a capillary blood sample. All patients using the POCT method replied that they preferred POCT to venepuncture, with only 1 patient switching back to venepuncture due to lack of confidence in the POCT INR result. Sixty-three patients attend for INR testing at the nearest government health centre, 19 patients test the INR at the ACC clinic at MDH and 18 test the INR at their own residence by a nurse (n=16) or family physician (n=2).

Patients testing the INR by POCT confirmed that the required warfarin dose is being communicated during the consultation, while patients who test the INR by venepuncture have the warfarin dose communicated by a telephone call on the same day, followed by a written prescription received by postal mail. When asked about the preferred method

for warfarin dose communication, 87 patients preferred a face-to-face consultation during which dose instructions are provided (Figure 3.11).

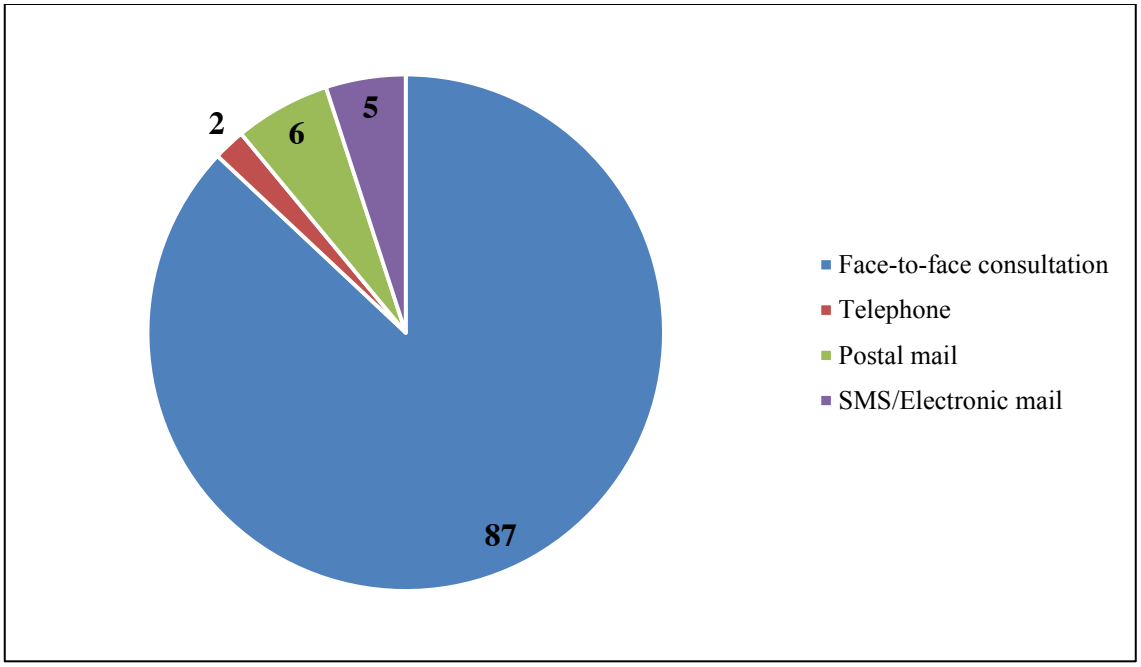


Figure 3.11: Preferred method for warfarin dose communication (N=100)

3.7.1 Patient satisfaction with current anticoagulation service

A mean rating score of 4.38 out of 5 (range 1-5) was obtained when patients were asked to rate the quality of the anticoagulation service currently being provided at the government health centres. Fifty-three patients stated that they are 'very satisfied' (score of 5) with the current service (Figure 3.12).

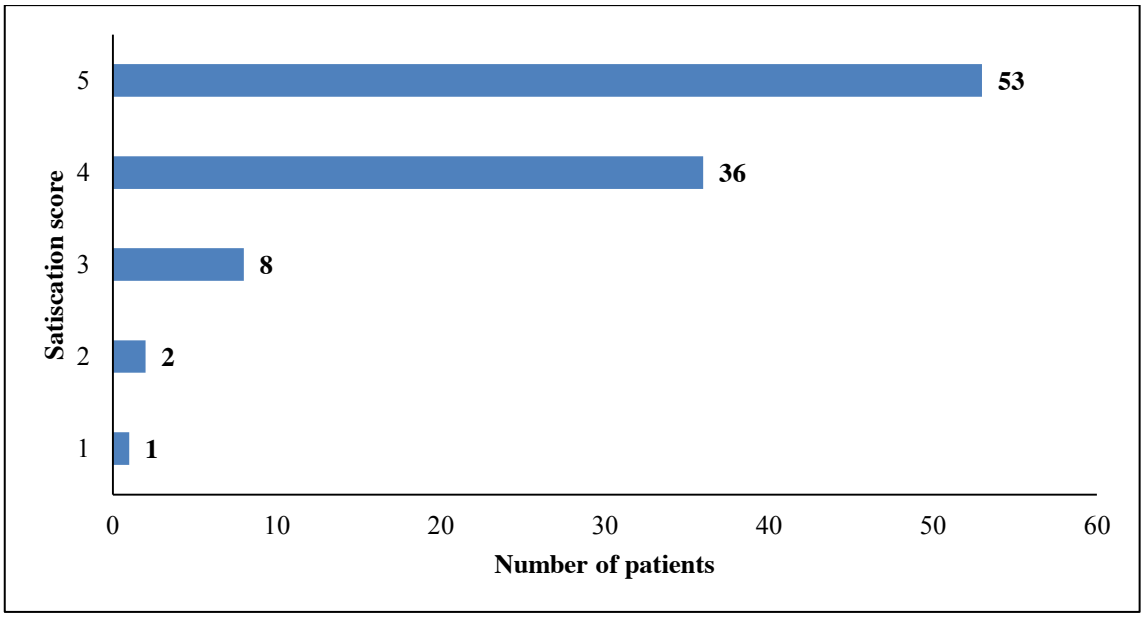


Figure 3.12: Satisfaction with current anticoagulation management service (N=100)

A mean rating score of 2.04 out of 5 (range 1-5) was obtained when patients were asked to rate their satisfaction with the advice and information provided on anticoagulation management during the INR testing appointment, with 41 patients stating that they are not satisfied (Figure 3.13).

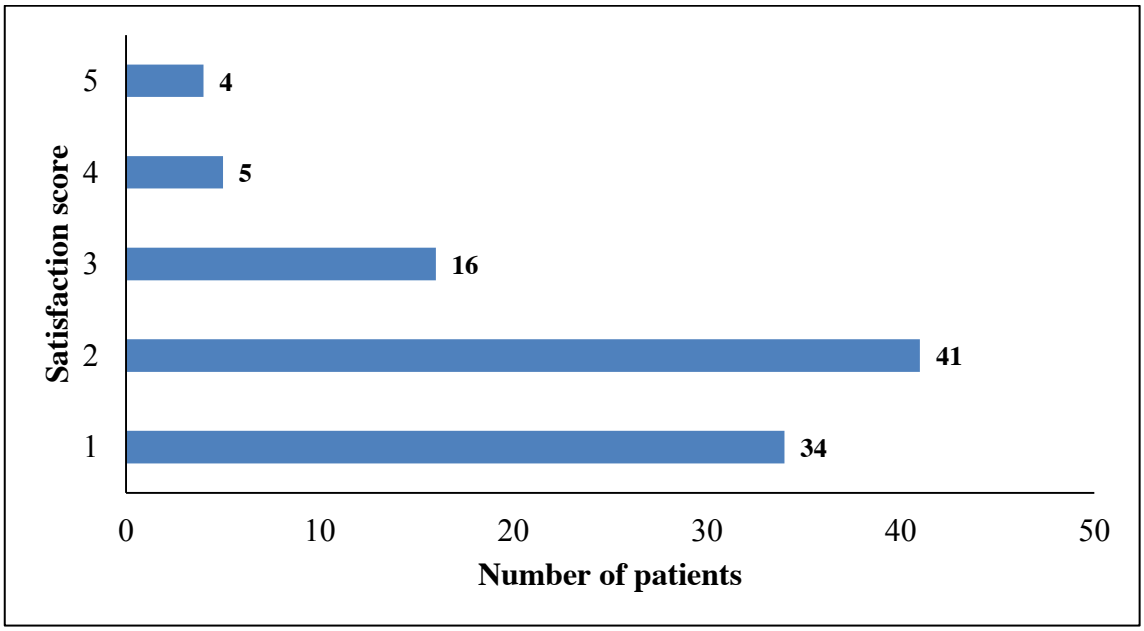


Figure 3.13: Satisfaction with advice and information provided at anticoagulation clinics (N=100)

Seventy-three patients stated that no counselling on anticoagulation was provided when initially prescribed warfarin. Of the 27 patients who were provided with initial counselling, 15 stated that advice was provided by a nurse, followed by a physician (n=8) and a pharmacist (n=4).

3.7.2 Patient suggestions to improve current anticoagulation service

Thirty-five patients stated the need for change or improvement to the current anticoagulation system. Thirteen patients who are currently having INR tested by venepuncture were willing to change to POCT INR testing (Table 3.9).

Table 3.9: Patient suggestions to improve current anticoagulation service (n=35)

Suggestion	Number of patients
Switch to POCT	**13**
Reduce waiting time for prescription	10
Provision of education	6
Increase service consistency	5
Reduce cost of NOACs	1

3.8 Polypharmacy

A total of 632 medications were reconciled, with a mean of 6.32 medications per patient (±2.76, range 1-16 medications). Seventy-six patients were taking 5 or more medications, 13 of whom were taking 10 or more medications (Table 3.10). A significant positive correlation between the number of medications, with age (Spearman correlation coefficient 0.24, $p<0.05$) and the number of comorbidities (Spearman correlation coefficient 0.702, $p<0.05$) was observed.

Table 3.10: Chronic medications (N=100)

Number of chronic medications	Number of patients
1	3
2	2
3	8
4	11
5	**21**
6	13
7	12
8	13
9	4
10	4
11	2
12	6
16	1

The medications included prescription-only items, OTC preparations and supplements. Sixty-seven percent (n=423) of the medications were classified in the cardiovascular system category (Table 3.11). After anticoagulants (warfarin), the top prescribed medications were diuretics (10.4%, n=66), ACE inhibitors (8.5%, n=54) and statins (8.2%, n=52).

Table 3.11: Classification of chronic medications (N=632)

BNF Classification	Number of medications	Percentage (%)
Cardiovascular system	**423**	**66.9**
Endocrine system	51	8.1
Blood and nutrition	45	7.1
Gastro-intestinal system	37	5.9
Nervous system	36	5.7
Respiratory system	14	2.2
Musculoskeletal system	10	1.6
Genito-urinary system	6	1.1
Eye conditions	5	0.8
Malignant disease	5	0.8

3.8.1 Drug interactions

A total of 698 drug-drug interactions (DDIs) were identified (mean 6.98 per patient, range 0-20), with 98 interactions classified as 'serious', 517 as 'significant' and 83 as 'minor'. Only 11 patients had no DDIs. A significant positive correlation between the number of chronic medications and the occurrence of DDIs was observed (Spearman Correlation Coefficient 0.822, $p<0.05$). Identified co-prescribed medications that may increase bleeding risk associated with warfarin included; amiodarone (n=17), levothyroxine (n=13), aspirin (n=9), paroxetine (n=7) and fluvoxamine, dipyridamole and clopidogrel (all n=1).

3.9 Analysis of identified drug-related problems

A total of 481 DRPs were identified during the MUR sessions (mean 4.81 ±1.83, range 0-9 DRPs per patient). Twenty-two patients had 5 DRPs and only 1 patient had no DRPs identified (Figure 3.14).

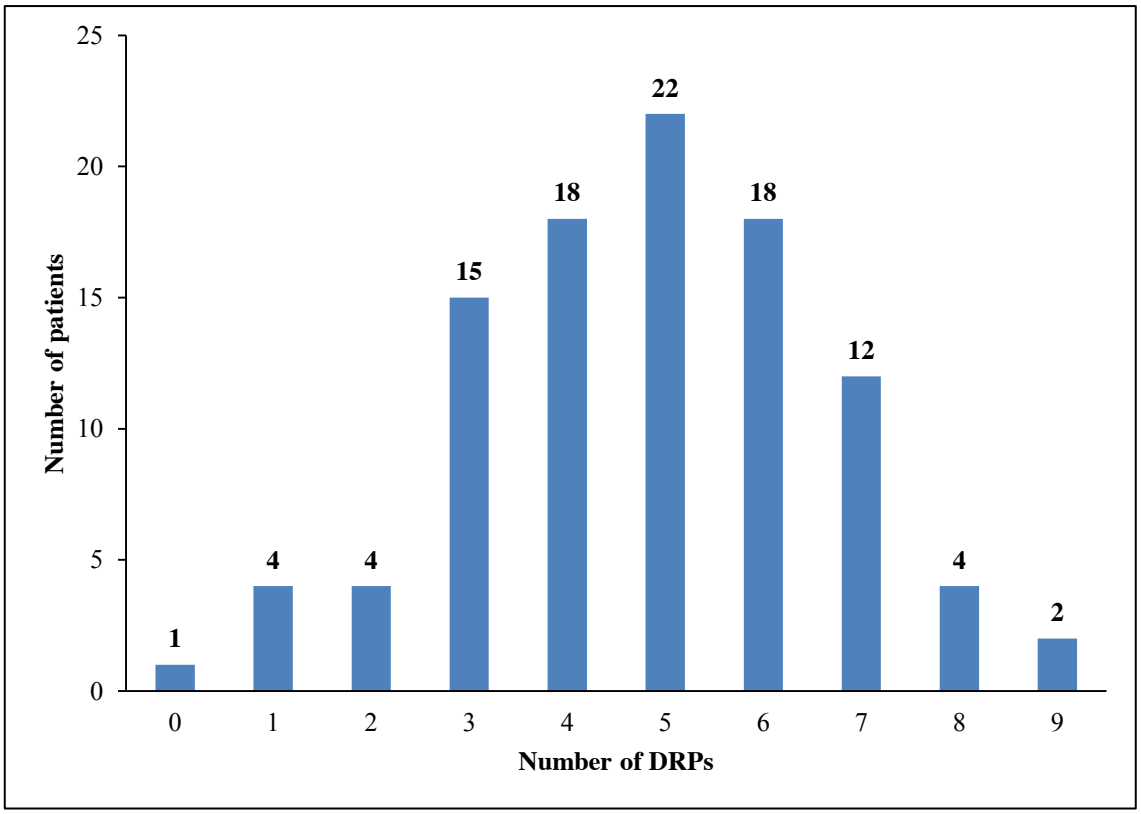


Figure 3.14: Number of drug-related problems per patient (N=481)

3.9.1 Types of drug-related problems according to DOCUMENT classification

Need for monitoring (30%, n=145), lack of compliance (20%, n=97) and need for patient education (19%, n=90) were the top three DRPs identified (Figure 3.15).

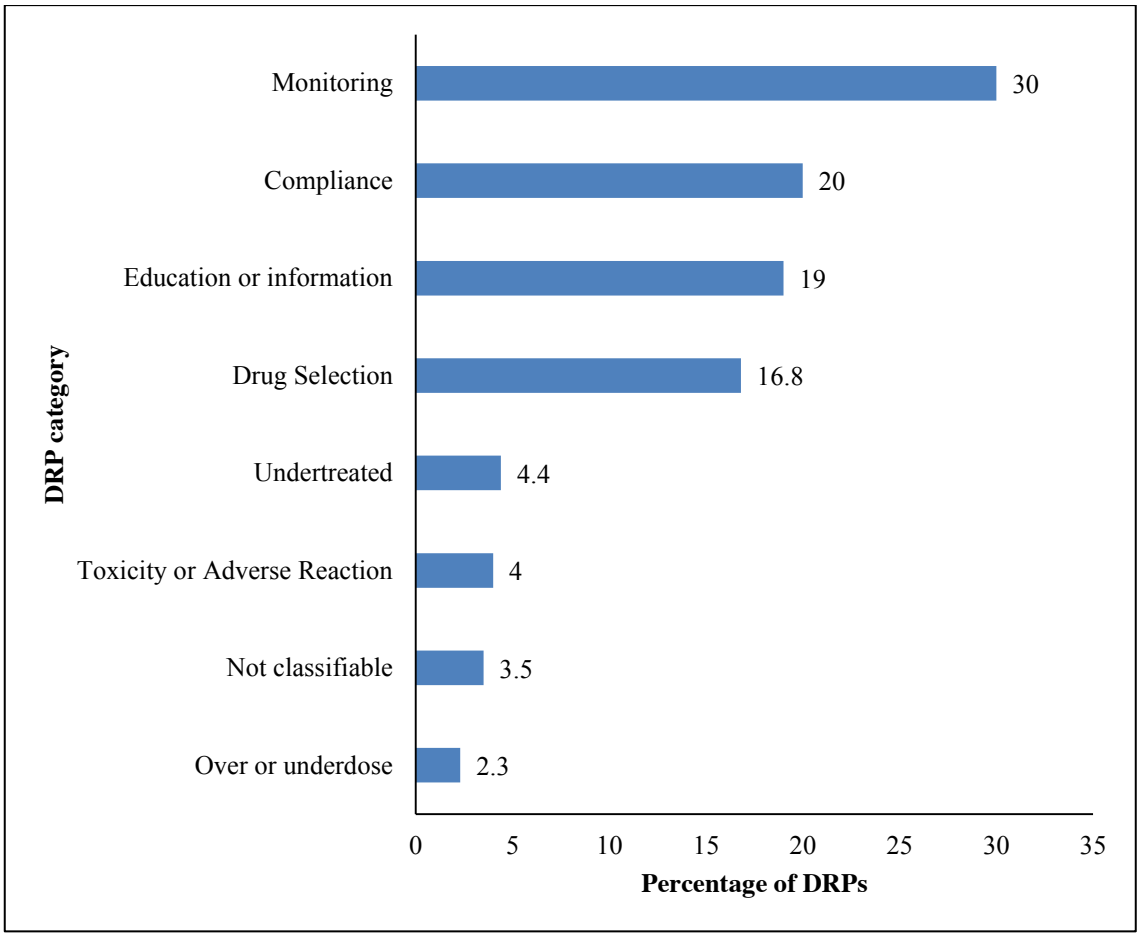


Figure 3.15: Type of drug-related problems identified (N=481)

With regards to DRPs classified in the 'Monitoring' category (30%, n=145), 87 DRPs (18.1%) were classified under 'Laboratory monitoring' and 55 DRPs (11.4%) were classified under 'Non-laboratory monitoring'. Out of the 55 DRPs classified as 'Non-laboratory monitoring', 53 patients required blood pressure (BP) monitoring since they were being prescribed a combination of drugs that may affect BP and 2 patients required frequent POC glucose testing. Three DRPs were classified as 'Other monitoring problem 'No INR requested after administration of interacting medication' since the patients were prescribed a short course of drugs which interact with warfarin namely, antibiotics (n=2) and NSAIDs (n=1) without INR testing (Table 3.12).

Table 3.12: Type and frequency of drug-related problems classified in 'Monitoring' category (n=145)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Laboratory monitoring	**87**	**60.0**	**18.1**
Non-laboratory monitoring	55	38.0	11.4
Other monitoring problem: No INR requested after administration of interacting medication	3	2.0	0.6

For DRPs classified in the 'Compliance' category (20%, n=97), 45 DRPs (9.4%) were related to warfarin administration. The top compliance problem was 'Under-use of medication' (11%, n=53), followed by 'Other: Suboptimal timing of medication administration' (3.7%, n=18) and 'Erratic use of medication' (2.1%, n=10) (Table 3.13). Twenty-five DRPs classified in the 'Under-use of medication' were non-adherence to the daily warfarin dose, followed by non-adherence to diuretics (n=8). Seven of the 18 DRPs associated with 'Suboptimal timing of medication administration' were related to levothyroxine since patients were not aware of the correct administration (Appendix 7).

Table 3.13: Type and frequency of drug-related problems classified in 'Compliance' category (n=97)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Under-use by consumer	**53**	**54.6**	**11.0**
Other: Suboptimal timing of medication administration	18	18.6	3.7
Erratic use of medication	10	10.3	2.1
Over-use by consumer	6	6.2	1.2
Other: Difficulty in changing warfarin dose	5	5.2	1.0
Intentional drug misuse	2	2.1	0.4
Other: Patient non-compliant with INR tests	2	2.1	0.4
Difficulty in using dosage form	1	1.0	0.2

For DRPs classified in the 'Education or information' category (19%, n=90), 82 DRPs (9.4%) were related to anticoagulation therapy (17%). Seventy-two DRPs (15%) were classified in the subcategory 'Other: Patient education to address gaps identified from the knowledge test', followed by 16 DRPs classified in the subcategory 'Consumer requests drug information' (Table 3.14). Eleven of the 16 DRPs classified as 'Consumer requests drug information' were related to the novel oral anticoagulants (NOACs) (Appendix 7).

Table 3.14: Type and frequency of drug-related problems classified in 'Education or information' category (n=90)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Other: Patient education to address gaps identified from the knowledge test	**72**	**80.0**	**15.0**
Consumer requests drug information	16	17.8	3.3
Consumer requests disease management advice	2	2.2	0.4

Eighty-one (16.8%) DRPs were classified as 'Drug selection' issues, 35 (7.3%) of which were related to warfarin. Sixty-three (13.1%) of the 'Drug selection' DRPs were classified as 'Drug interaction' followed by 14 DRPs (2.9%) classified as 'No indication apparent' (Table 3.15). Twenty-six of the 63 DRPs classified as 'Drug interaction' had the potential to increase bleeding risk. Nine (1.9%) of the 14 (2.9%) DRPs classified as 'No apparent indication' were associated with the use of omeprazole (Appendix 7).

Table 3.15: Type and frequency of drug-related problems classified in 'Drug Selection' category (n=81)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Drug Interaction	**63**	**77.8**	**13.1**
No indication apparent	14	17.3	2.9
Wrong Drug	1	1.2	0.2
Inappropriate dosage form	1	1.2	0.2
Other: Need for treatment	1	1.2	0.2
Other: Duration of treatment	1	1.2	0.2

Twenty-one (4.4%) DRPs were classified in the 'Undertreated' category, with only 1 DRP related to warfarin. Seven DRPs were classified as 'Condition undertreated' and involved 4 different conditions, namely, anxiety (n=3), heart failure (n=2), gout and hypertension (both n=1). Seven DRPs were classified as 'Untreated conditions' and involved 7 different conditions namely, anxiety, arrhythmia, bleeding haemorrhoids, hypertension, gastro-oesophageal reflux disease and urinary incontinence (all n=1). Seven DRPs were classified as 'Preventive therapy required' namely patient on steroids with no osteoprotection (n=3), patient on a combination of drugs that increase risk of upper gastrointestinal bleeding without gastroprotection (n=2), and need for compression stockings to improve blood circulation in the lower extremities (n=1) (Table 3.16).

Table 3.16: Type and frequency of drug-related problems classified in 'Undertreated' category (n=21)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Condition undertreated	7	33.3	1.5
Condition untreated	7	33.3	1.5
Preventive therapy required	7	33.3	1.5

Nineteen (4%) DRPs were classified in the category 'Toxicity and Adverse Reactions', with antihypertensives and statins having the highest number of ADRs, 6 and 4 respectively (Appendix 7). Three ADRs identified were related with warfarin use. Seventeen (3.5%) DRPs were classified in the category 'Not classifiable'. Eleven of the 17 DRPs were classified in the 'Smoking cessation' subcategory (Table 3.17).

Table 3.17: Type and frequency of drug-related problems classified in 'Not classifiable' category (n=17)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Smoking cessation	**11**	**64.7**	**2.3**
Alcohol binging	4	23.5	0.8
Obesity	1	5.9	0.2
Confirm INR target range	1	5.9	0.2

Eleven (2.3%) DRPs were classified in the 'Over or underdose' category, 2 of which were related to warfarin. Six DRPs were classified in the 'Prescribed dose too high' and involved 5 medications namely, benzodiazepines (n=4), gliclazide (n=1) and digoxin (n=1). Five DRPs were classified in the 'Incorrect or unclear dosing instructions' and involved 4 medications namely, warfarin (n=2), digoxin, furosemide and metformin (all n=1) (Table 3.18).

Table 3.18: Type and frequency of drug-related problems classified in 'Over or underdose' category (n=11)

Subcategory	Number of DRPs	Percentage (%)	Percentage of total DRPs (%)
Prescribed dose too high	**6**	**5.5**	**1.2**
Incorrect or unclear dosing instructions	5	4.5	1.0
Prescribed dose too low	0	0.0	0.0

3.9.2 Medications causing drug-related problems

Cardiovascular drugs were responsible for 84% of DRPs identified (n=404) (Table 3.19).

Table 3.19: Drug-related problems classified according to medication classification (N=481)

Medication classification	Number of DRPs	Percentage of total DRPs (%)
Cardiovascular system	**404**	**84.0**
Endocrine system	24	5.0
Gastro-intestinal system	18	3.7
Nervous system	17	3.5
Blood and nutrition	9	1.9
Genito-Urinary system	5	1.0
Respiratory system	4	0.8

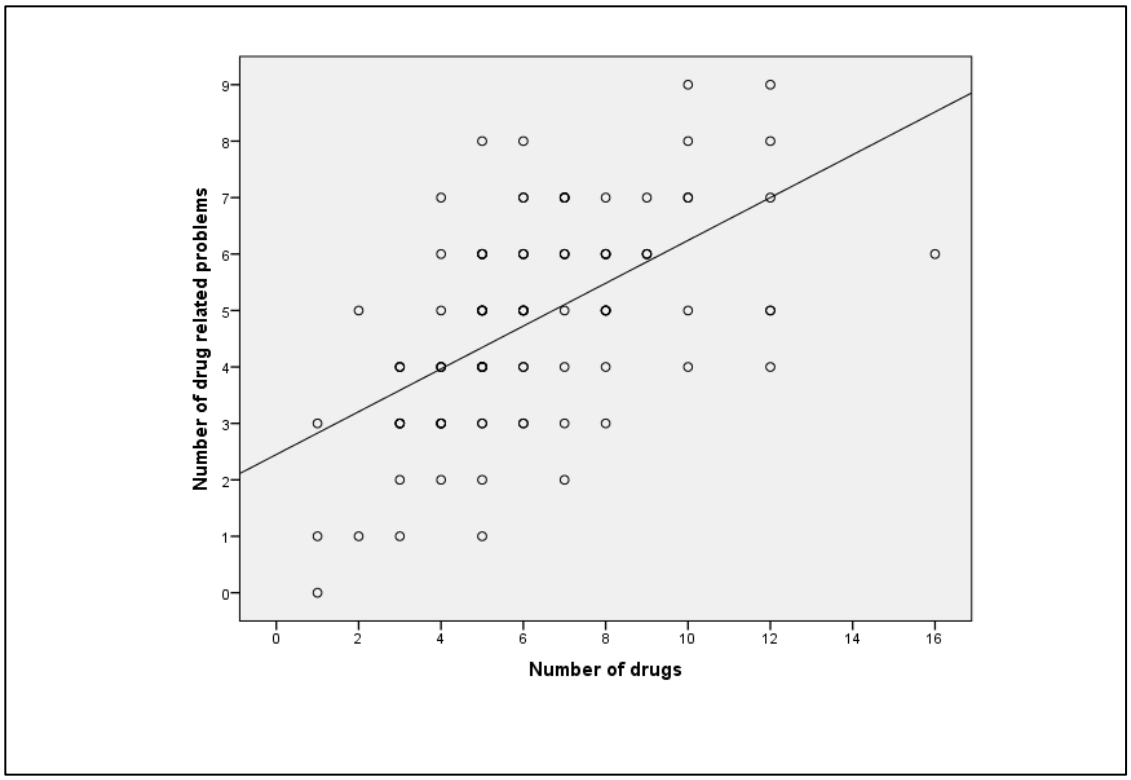
Forty percent of the DRPs were warfarin-related (n=190). Ninety patients had at least one DRP which was related to warfarin, with a mean of 1.9 warfarin related-DRPs per patient (range 0-4). The top warfarin-related DRPs were the need for education and information on anticoagulation (17%, n=82), followed by compliance issues (9.8%, n=47) and drug selection issues (7.3%, n=35) (Table 3.20).

Table 3.20: Type and frequency of warfarin-related drug-related problems (n=190)

DRP Category	Number of warfarin-related DRPs	Percentage of total DRPs (%)
Education or information	**82**	**17.0**
Compliance	47	9.8
Drug Selection	35	7.3
Not classifiable	16	3.3
Monitoring	4	0.8
Toxicity	3	0.6
Over or underdose	2	0.4
Undertreated	1	2.1

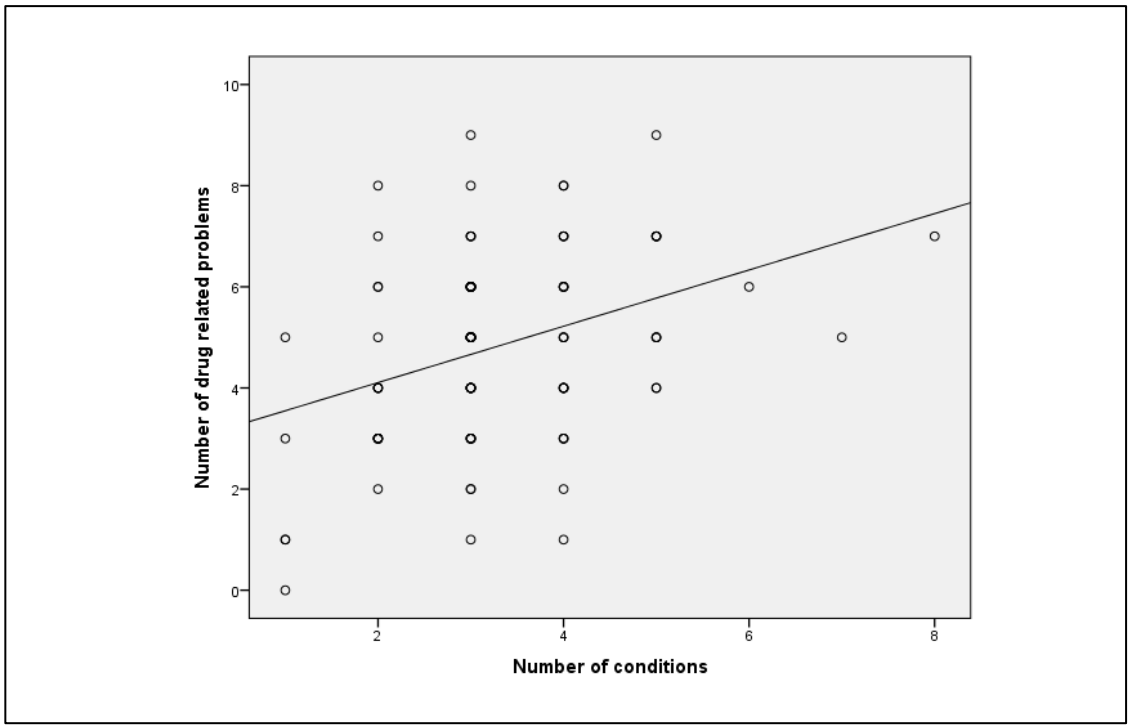
3.9.3 Factors influencing number of drug-related problems

Prevalence of DRPs was associated with a higher number of chronic medications, comorbidities and older age ($p<0.05$). These relationships were confirmed with the Spearman Correlation Coefficient test (Figure 3.16 to 3.18).



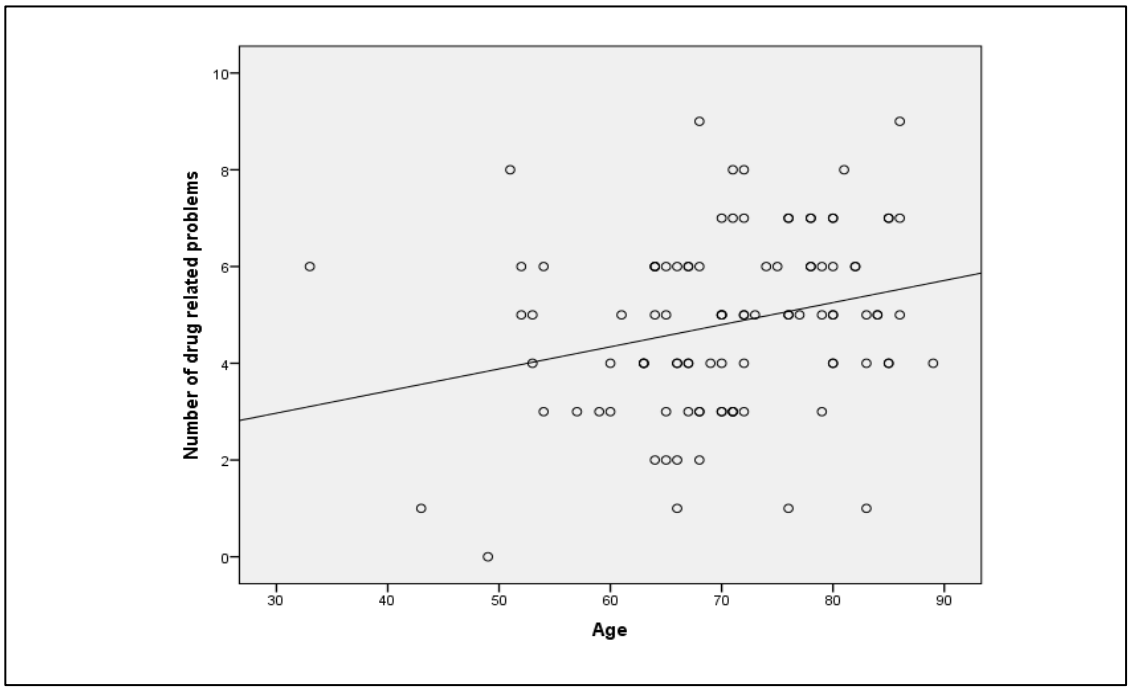
Spearman Correlation 0.583, $p<0.001$

Figure 3.16: Correlation between number of drug-related problems and number of chronic medications per patient



Spearman Correlation 0.327, p=0.001

Figure 3.17: Correlation between number of drug-related problems and number of comorbidities per patient



Spearman Correlation 0.285, p=0.040

Figure 3.18: Correlation between number of drug-related problems and age

An inverse relationship between the warfarin knowledge test score pre-intervention and the number of warfarin-related DRPs was observed (Spearman Correlation=-0.241, $p<0.05$).

3.9.4 Clinical significance of identified drug-related problems

Seventy-six percent (n=366) of the interventions were classified as 'Intervention is significant and results in an improvement in patient care' (Table 3.21).

Table 3.21: Clinical significance of identified drug-related problems (N=481)

Clinical significance classification	Number of DRPs	Percentage of total DRPs (%)
Intervention is detrimental to patient health	0	0.0
Intervention is of no significance to patient care	0	0.0
Intervention is significant but does not result in an improvement in patient care	14	2.9
Intervention is significant and results in an improvement in patient care	**366**	**76.1**
Intervention is very significant and prevents major organ damage or an adverse reaction of similar importance	99	20.6
Intervention is potentially life-saving	2	0.4

3.10 Recommendations and clinical interventions

For each identified DRP a clinical intervention was recommended. A total of 481 clinical interventions were recommended by the pharmacist researcher. Provision of information (37.6%, n=181), need for monitoring (30.8%, n=148) and referral required (29.5%, n=142) were the top recommended clinical interventions (Table 3.22).

Table 3.22: Pharmacist researcher's recommendations classified according to the DOCUMENT classification system (N=481)

Category	Number of DRPs	Subcategory	Number of DRPs
Provision of information	**181**	**Education or counselling session**	**155**
		Recommended dose administration aid	26
Monitoring	148	Monitoring: Laboratory	92
		Monitoring: Non-laboratory	56
Referral required	142	Refer to prescriber: Close assessment of the risk benefit ratio of the treatment	64
		Refer to prescriber: Start new drug	20
		Refer to prescriber: Change dosage	19
		Refer to prescriber: Confirm dosage	18
		Refer to prescriber: Stop drug	12
		Refer to prescriber: Change drug	4
		Refer to prescriber: Change instruction of use	2
		Other: Nutritionist	1
		Other: ACC	2
Change of therapy	10	Other: Drug stopped	7
		Dose decrease	1
		Drug change	1
		Drug formulation change	1

Two hundred thirty-four (48.6%) recommendations were referred for consideration by the physician, 116 (24.1%) clinical interventions were performed by the pharmacist researcher during the MUR session, 101 (21%) recommendations were discussed with the patients and 27 (5.6%) recommendations were referred for intervention by the community pharmacist. Two DRPs were referred for consideration by the staff at the ACC and 1 patient was referred to a nutritionist. Recommendations referred for physician attention were related to 'Monitoring' (18.1%, n=87) and 'Drug selection' issues (15.6%, n=75), while interventions by the pharmacist researcher were related to 'Education or information' (18.7% n=90) (Table 3.23).

Table 3.23: Person responsible to intervene and solve identified drug-related problem (N=481)

	Consideration by				
DRP category	**Physician**	**Pharmacist researcher**	**Patient**	**Community pharmacist**	**Other[a]**
Drug selection	75	5	0	1	0
Over or underdose	10	0	0	0	1
Compliance	22	5	43	**26**	1
Undertreated	20	1	0	0	0
Monitoring	**87**	0	**58**	0	0
Education or information	0	**90**	0	0	0
Not classifiable	1	15	0	0	1
Toxicity and adverse drug reaction	19	0	0	0	0
Total	234	116	101	27	3

[a]Other: ACC, nutritionist

3.10.1 Outcome of implemented recommendations

Of the 481 DRPs identified during the MUR session a total of, 475 DRPs were assessed during the follow-up session since one patient withdrew from the study. Of these, 397 (83.6%) recommendations were accepted, while the other 78 (16.4%) recommendations were rejected. The top three accepted pharmacist researcher recommendations were 'Monitoring' (35.6%, n=169), 'Change in treatment' (16.8%, n=80) and improvement in 'Compliance' (13.1%, n=62) (Table 3.24).

Table 3.24: Outcomes of clinical recommendations (n=475)

	Action by						
Outcome of clinical recommendation	**Physician**	**Pharmacist researcher**	**Patient**	**Community pharmacist**	**Other[a]**	**Number of recommendations**	**Percentage of recommendations (%)**
Monitoring	**122**	0	**47**	0	0	**169**	35.6
Change in treatment	60	7	13	0	0	80	16.8
Improved compliance	7	3	33	**19**	0	62	13.1
Improved knowledge	0	**61**	0	0	0	61	12.8
Dose administration aid	0	0	0	4	0	4	0.8
Advice taken into consideration	3	12	3	1	**2**	21	4.4
No action	40	31	3	3	1	78	16.4
Total	232	114	99	27	3	475	

[a]Other: ACC, nutritionist

The 'Difference between two proportions test' indicated that the percentage of accepted recommendations significantly exceeded the percentage of rejected recommendations ($p<0.05$) (Table 3.25). The percentage of accepted recommendations by each person responsible to intervene exceeded significantly the percentage of rejected recommendations, since p-values (expect 'Other') were less than the 0.05 level of significance.

Table 3.25: Accepted recommendations according to person responsible to intervene (n=475)

Person responsible to intervene	Total number of recommendations	Number of implemented recommendations	Percentage of recommendations accepted by responsible person (%)	z-score	p-value
Physician	**232**	**192**	82.8	14.11	<0.001*
Pharmacist researcher	114	83	72.8	6.89	<0.001*
Patient	99	96	**97**	13.22	<0.001*
Community Pharmacist	27	24	88.9	5.72	<0.001*
Other[a]	3	2	66.7	0.82	00.412
Total	475	397	83.6	20.70	<0.001*

[a]Other: ACC, nutritionist
*p<0.05: Statistically significant

Of the 232 recommendations referred for physician consideration, 194 (82.9%) were considered and action to improve medication safety and efficacy was taken. One hundred and two of the accepted recommendations by physicians resulted in referral for required 'Laboratory monitoring' (30.7%), followed by 'Changes in treatment' (15.1%, n=60) and 'Improved compliance with treatment' (1.8%, n=7).

Improvement in patient outcomes was observed in 83 of the 114 DRPs identified during the MUR session which required the pharmacist researcher's intervention. In 61 patients the counselling and advice provided by the pharmacist researcher resulted in improvement in patient knowledge.

Of the 99 recommendations to be considered by the patient, 96 were accepted. Thirteen recommendations were further referred to the physician for action. Forty-seven interventions resulted in adherence to required non-laboratory monitoring, followed by improved compliance to treatment (n=33) and changes in treatment (n=13).

Twenty-four of the 27 recommendations referred for consideration by the community pharmacist were implemented. Use of the warfarin dosing calendar in the 'Anticoagulation and Medication Profile' (Appendix 2) resulted in improved warfarin adherence in 19 of the 25 patients who missed at least a warfarin dose pre-intervention, while the community pharmacist started providing the service of dose administration aid (DAA) to 4 patients. Change in dosage formulation from a 20mg to 10mg tablet to avoid the need of halving a tablet was also implemented by the community pharmacist (n=1).

3.10.2 Unsolved recommendations

Eighty-two percent of DRPs classified in the 'Not classifiable' category (n=14) remained unsolved (Table 3.26). The 'difference between two proportions test' indicated that the percentage of unsolved recommendations classified in the 'Not Classifiable' category significantly exceeded the percentage of accepted recommendations ($p<0.05$), while the percentage of accepted recommendations classified in the 'Drug Selection', 'Education or information', 'Adverse Reaction', 'Compliance' and 'Monitoring' categories exceeded significantly the percentage of rejected recommendations ($p<0.05$).

Table 3.26: Recommendations which were not implemented per drug-related problems category (n=475)

DOCUMENT category	Number of identified DRPs	Number of unsolved DRPs	Percentage of recommendations not accepted	z-score	p-value
Not classifiable	17	14	**82.4**	3.77	<0.001*
Over or underdose	11	5	45.5	0.43	0.668
Undertreated	21	9	42.9	0.92	0.352
Drug Selection	81	23	28.4	5.50	<0.001*
Education or information	90	18	20.0	8.05	<0.001*
Adverse Reaction	19	2	10.5	4.87	<0.001*
Compliance	97	6	6.2	12.21	<0.001*
Monitoring	145	2	1.4	16.56	<0.001*

*p<0.05: Statistically significant

The DOCUMENT subcategories ‘drug interactions’ (2.3%, n=11), ‘smoking cessation’ (2.1%, n=10) and ‘no indication apparent’ (2.1%, n=10) were the subcategories with the most rejected recommendations (Table 3.27).

Table 3.27: Unsolved drug-related problems classified according to DOCUMENT subcategories (n=78)

Code	DRP category	DRP subcategory	Number of unsolved DRPs
D	**Drug selection**	Drug interaction	**11**
		No indication apparent	10
		Other: Need for treatment	1
		Other: Duration of treatment	1
O	Over or underdose	Prescribed dose too high	4
		Incorrect or unclear dosing instructions	1
C	Compliance	Under-use by consumer	6
U	Undertreated	Condition untreated	5
		Condition undertreated	3
		Preventive therapy required	1
M	Monitoring	Laboratory monitoring	2
E	Education or information	Other: Patient education to address certain gaps identified from the knowledge test	9
		Consumer requests drug information	8
N	Not classifiable	Smoking cessation	10
		Alcohol binging	3
		Obese	1
T	Toxicity	Adverse reaction	2

Forty of the 232 recommendations referred for physician attention remained unsolved, of which 21 (9%) were not reported to the physician by the patient and 19 (8.1%) were rejected by the physician after being informed by the patient. Six of the 19 rejected recommendations were a suggestion to discontinue omeprazole due to 'No apparent indication' (Table 3.28).

Table 3.28: Recommendations not accepted by physicians (n=19)

Recommendation	Number of unsolved DRPs	Description of DRP	Number of DRPs
Start new drug	6	Prevent GORD	2
		Uncontrolled cardiac condition	2
		Anxiety	1
		Urine incontinence	1
Stop drug	**6**	**No indication for omeprazole**	**6**
Change dosage	4	Tailoring of benzodiazepines	1
		Decrease statin dose due to interaction	1
		Overdose of digoxin	1
Close assessment to ensure risk/benefit	3	Drug causing bradycardia	2
		Drug causing myopathy	1

3.10.3 Treatment changes following pharmacist researcher recommendations

Eighty changes in patient treatment regimens were performed following recommendations suggested by the pharmacist researcher during the MUR session (Figure 3.19). A 2.1% reduction in the number of chronic medications was observed post-intervention, where 30 medications were discontinued and 17 medications were added, resulting in a total of 603 medications (mean 6 medications per patient). Two

patients of the 11 patients requesting information on NOACs, stopped warfarin and were switched to apixiban or rivaroxaban by the physician.

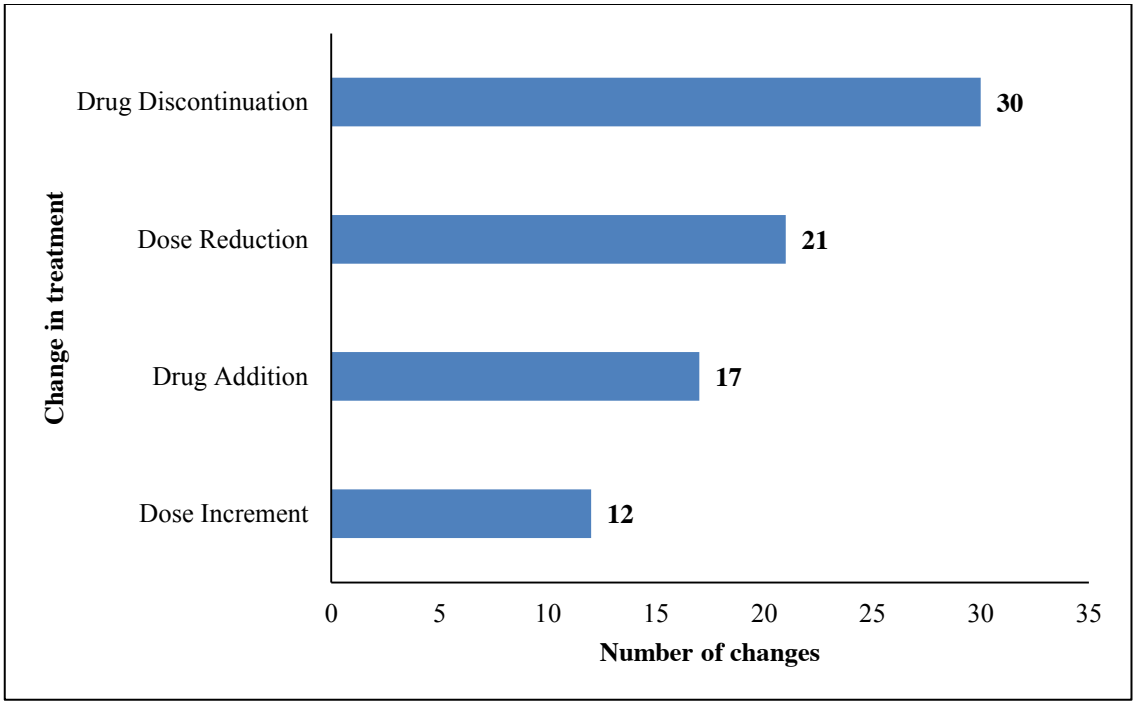


Figure 3.19: Treatment changes performed post-intervention (N=80)

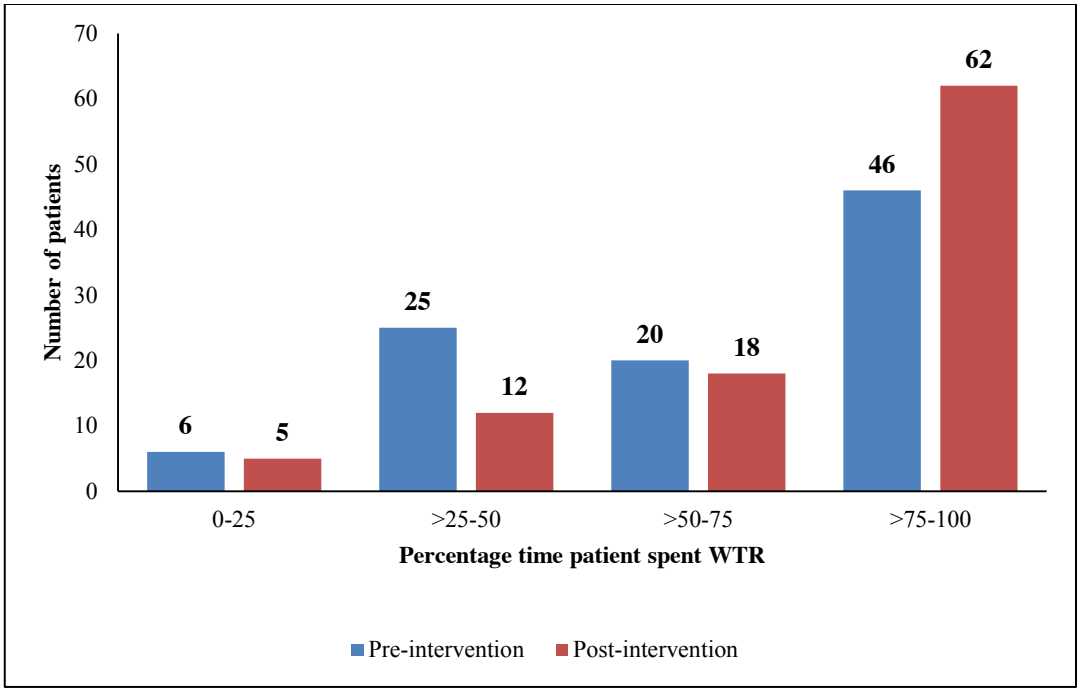
3.11 Analysis of time in therapeutic range

Prior to pharmacist intervention TTR was 68.74% (range: 0-100%). TTR significantly improved to 79.78% (range 6.5-100%) post-intervention (z-score-2.586, $p<0.05$) (Table 3.29).

Table 3.29: Time in therapeutic range (n=97)

	Percentage (%) number of days		
	Below Therapeutic Range	**Within Therapeutic Range**	**Above Therapeutic Range**
Pre-intervention	15.16	68.74	15.73
Post-intervention	10.01	79.77	10.33

Pre-intervention, 46 patients spent 75% of the time WTR, which increased to 62 patients post-intervention (Figure 3.20).



z-score -2.586, p=0.010

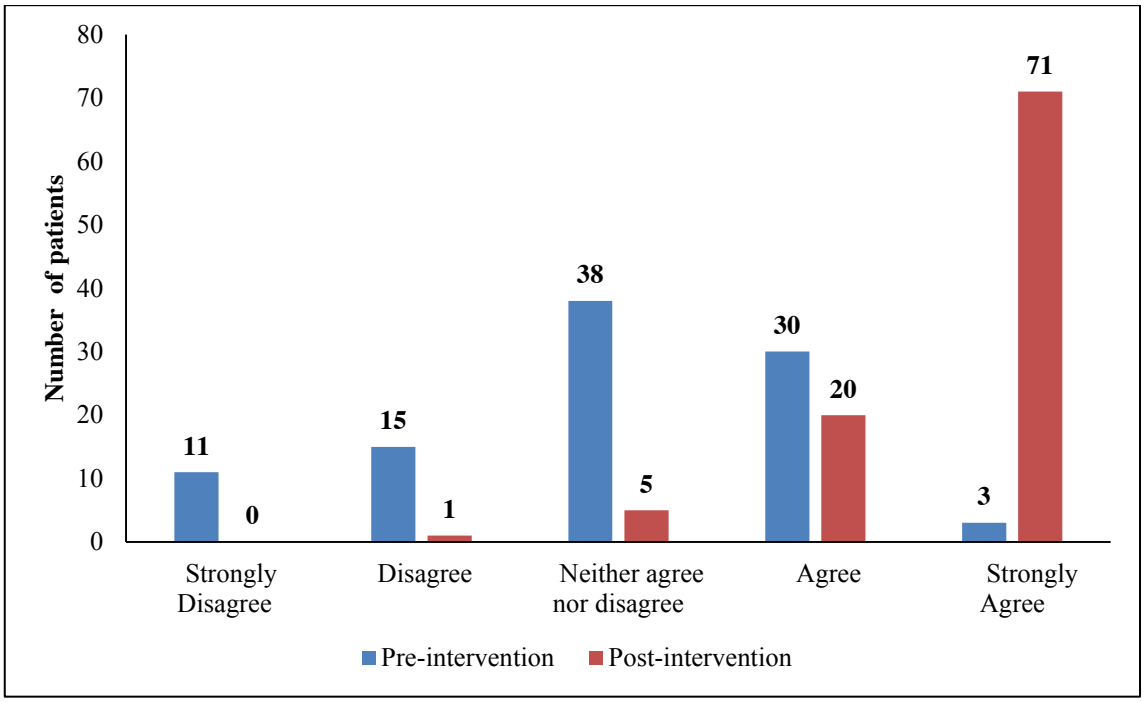
Figure 3.20: Comparison of time within therapeutic range pre- and post-intervention (n=97)

3.12 Patient perception on the role of the community pharmacist in medicine use review

The Wilcoxon signed rank test showed that the pharmacist researcher's intervention resulted in a statistically significant ($p<0.05$) change in patient perception on the role of the community pharmacist in therapeutic management and on the impact of pharmacist intervention with respect to anticoagulation therapy.

3.12.1 Perception of pharmacist competence in managing warfarin

Pre-intervention, only 33 patients stated being confident that a pharmacist can safely manage anticoagulation treatment. An improvement in patient confidence post-intervention was observed, with 91 patients stating that they 'agreed' or 'strongly agreed' that pharmacists are able to safely manage anticoagulation treatment (Figure 3.21). The mean score of the statement improved significantly ($p<0.05$) from 2.99 to 4.65 out of 5.

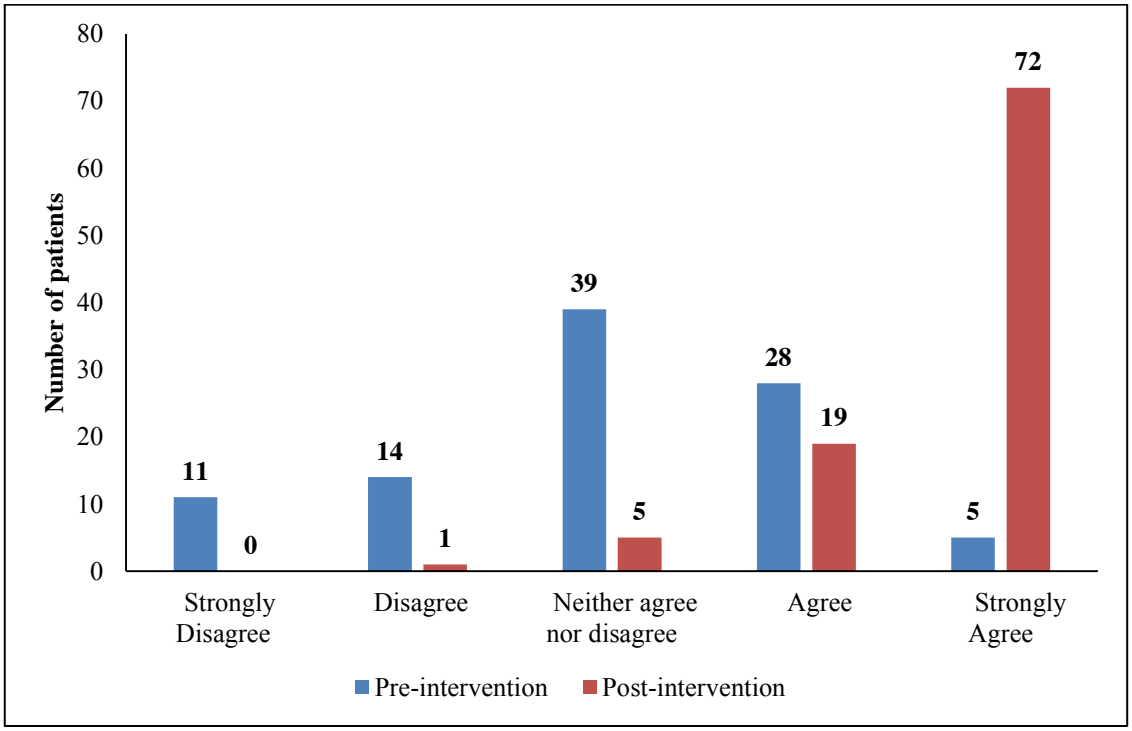


z-score -8.407, $p<0.001$

Figure 3.21: Patient perception on pharmacist competence to manage warfarin treatment (n=97)

3.12.2 Perception on benefits of pharmacist intervention

Pre-intervention, only 33 patients stated that they 'agreed' or 'strongly agreed' that pharmacist intervention will improve treatment outcomes in their overall health and contribute to better INR control. This increased to 91 patients post-intervention. The mean score of the statement significantly ($p<0.05$) improved from 3.02 pre-intervention to 4.67 out of 5 post-intervention (Figure 3.22).



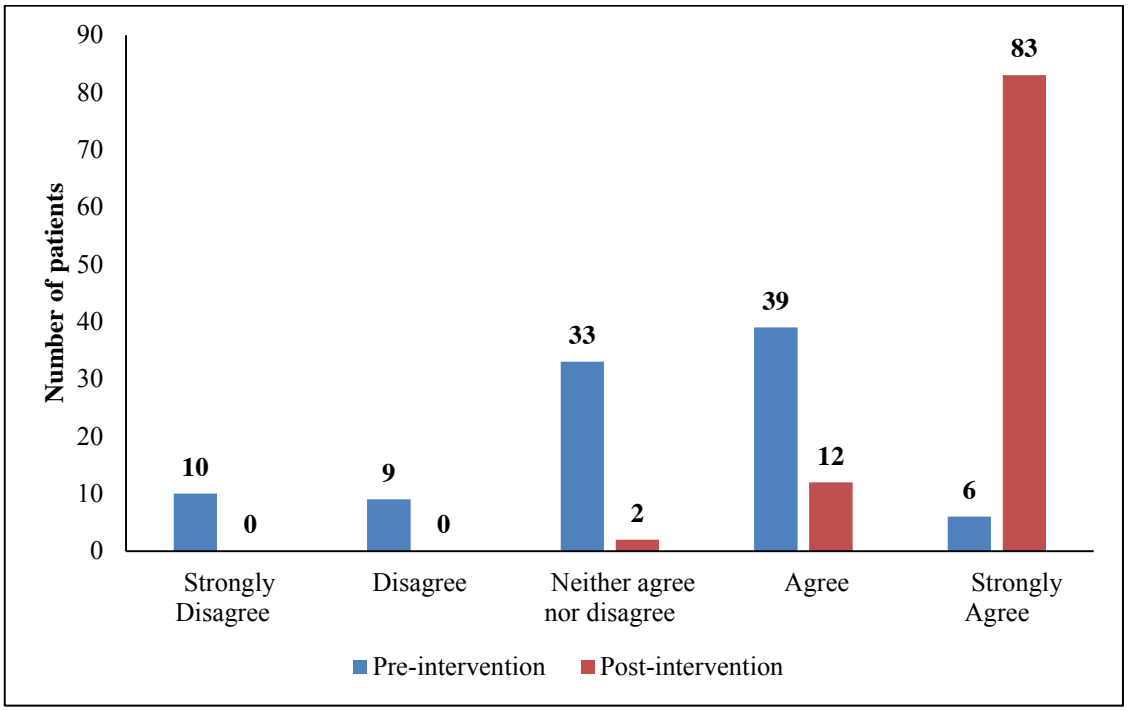
z-score -8.319, $p<0.001$

Figure 3.22: Patient perception on pharmacist competence to improve treatment outcomes (n=97)

3.12.3 Perception on pharmacist role in providing treatment advice

Pre-intervention, 45 patients stated that they 'agreed' or 'strongly agreed' that the pharmacist is able to provide treatment advice that will improve patient confidence in handling warfarin. Post-intervention the number of patients recognising that they will

benefit from the pharmacist's educational sessions increased to 95. A significant improvement ($p<0.05$) in the mean score of the statement from 3.22 pre-intervention to 4.84 out of 5 post-intervention was observed (Figure 3.23).

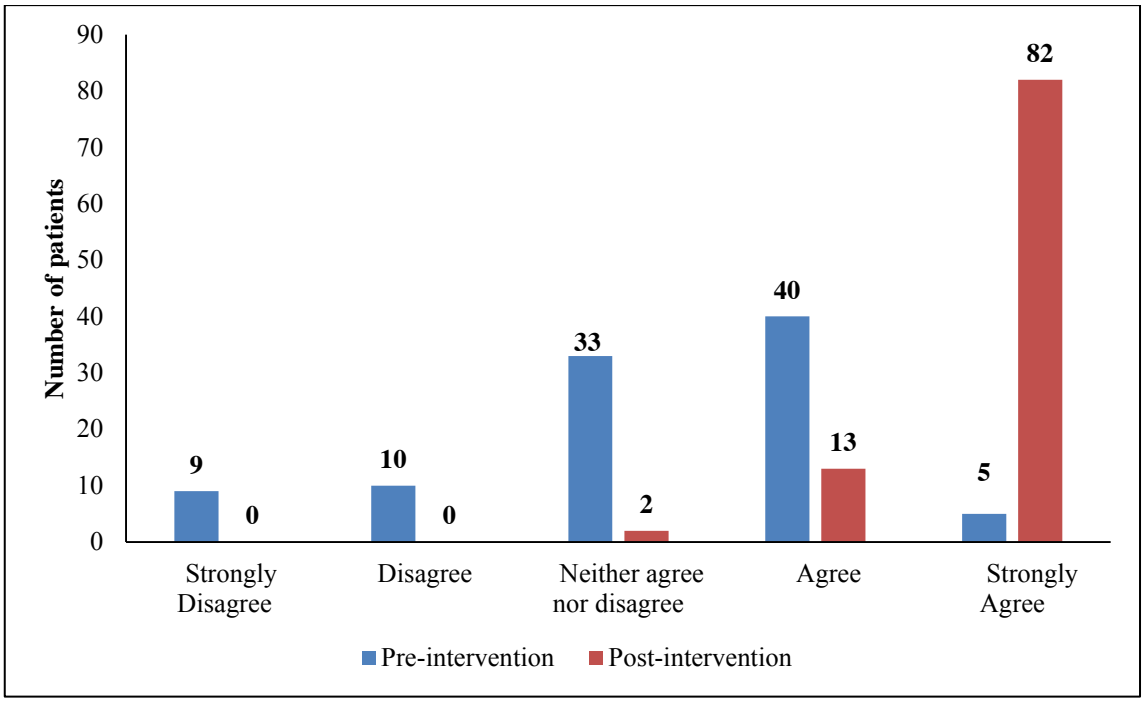


z-score -8.249, $p<0.001$

Figure 3.23: Patient perception on pharmacist competence to improve patient confidence in handling warfarin (n=97)

3.12.4 Perception on face-to-face interventions

Pre-intervention, 45 patients stated that they 'agreed' or 'strongly agreed' that the possibility to discuss warfarin treatment with a pharmacist when attending for INR testing will be beneficial. This increased to 95 patients post-intervention. A significant ($p<0.05$) improvement in the mean score of the statement from 3.23 pre-intervention to 4.82 out of 5 post-intervention was observed (Figure 3.24).

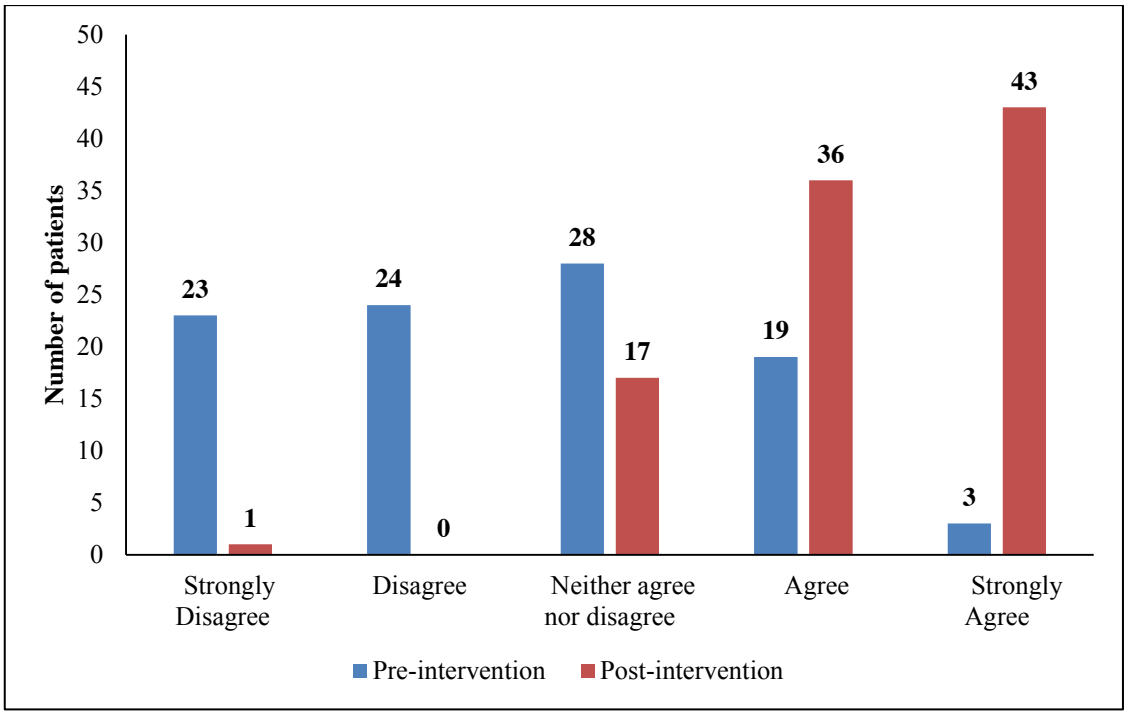


z-score -8.356, p<0.001

Figure 3.24: Patient perception on benefits of treatment discussion with pharmacist when attending for INR testing (n=97)

3.12.5 Perception on pharmacist role in warfarin dosing

The statement on patient acceptance of pharmacists performing warfarin dose adjustments obtained the lowest mean score, both pre- and post-intervention, 2.51 and 4.24 out of 5 respectively. Patient opinion on pharmacist competence to perform warfarin dose adjustments improved significantly post-intervention ($p<0.05$). The number of patients stating that they 'agreed' or 'strongly agreed' with warfarin dose adjustments performed by pharmacists increasing from 22 to 79 (Figure 3.25).

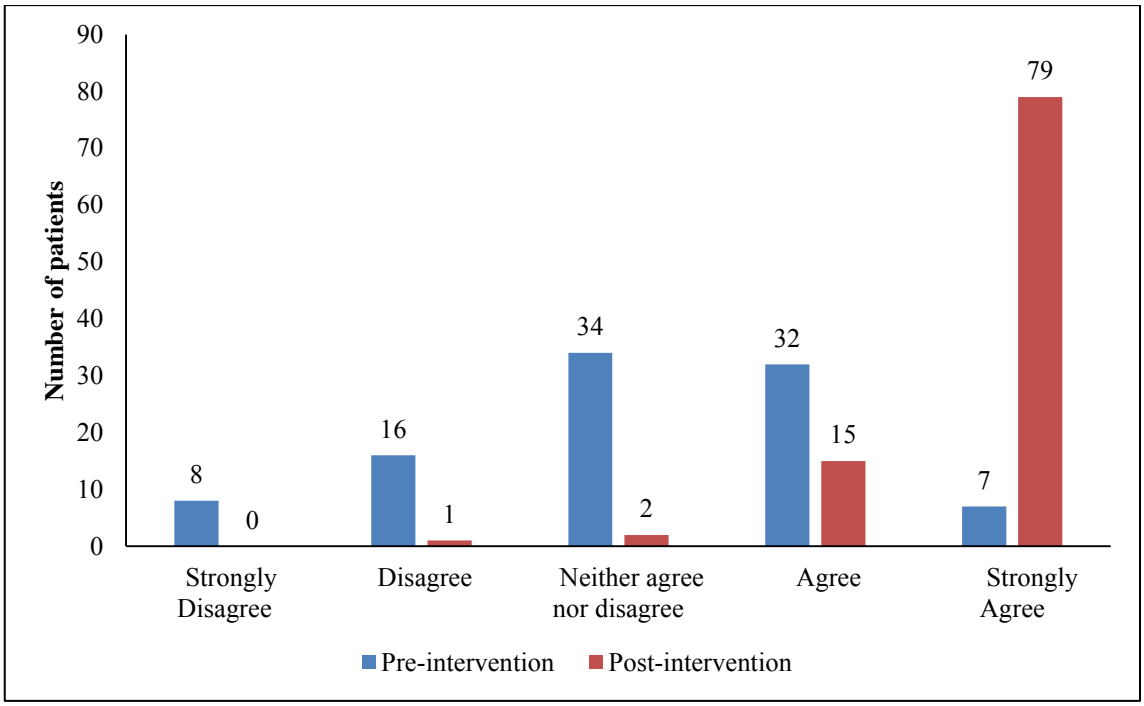


z-score -8.293, $p<0.001$

Figure 3.25: Patient perception on pharmacist competence to perform warfarin dosing (n=97)

3.12.6 Perception on pharmacist role in provision of medicine use review

Pre-intervention, 39 patients stated that they 'agreed' or 'strongly agreed' with medication review and provision of necessary recommendations by the pharmacist. After attending the pharmacist-led MUR sessions, the number of patients who agreed that the pharmacist is capable of performing MUR increased to 94. A significant improvement ($p<0.05$) in the mean score from 3.14 to 4.77 out of 5 was observed post-intervention (Figure 3.26).



z-score -8.308, p<0.001

Figure 3.26: Patient opinion on pharmacist role in medicine use review (n=97)

3.12.7 Perception on quality of life

Pre-intervention, 56 patients stated that they 'agreed' or 'strongly agreed' that warfarin affects quality of life. A high mean score of 3.84 out of 5 in the pre-intervention questionnaire demonstrated that patients agree that warfarin has a negative impact on quality of life. A significant positive improvement of patient perception on quality of life was observed post-intervention, where the mean score decreased to 3.27 out of 5 ($p< 0.05$).

Patients stated that the need for frequent warfarin dose adjustments complicates treatment, with the statement obtaining a mean score of 3.70 out of 5. Post-intervention, a significant decrease in patients who agreed that dose adjustments complicate treatment was observed, with the mean score decreasing to 3.14 out of 5 ($p<0.05$).

3.13 Patient satisfaction with pharmacist-led medicine use review

Patients were satisfied with the pharmacist researcher's contribution during the two clinical sessions and only 12 patients stated that no new information regarding their treatment was provided by the pharmacist researcher. Prior to the MUR session pre-intervention, 47 patients rated their anticoagulation knowledge as 'Fair' and only 7 patients rated their knowledge as 'Good' or 'Very good'. Post-intervention a statistically significant improvement in patient perception of their level of anticoagulation knowledge was observed ($p<0.05$) (Table 3.30).

Table 3.30: Patient rating of anticoagulation knowledge (n=97)

Knowledge rating	Number of patients pre-intervention	Number of patients post-intervention
Very Poor	15	0
Poor	28	5
Fair	**47**	**47**
Good	6	43
Very Good	1	2

z-score -7.407, $p<0.001$

3.13.1 Duration of clinical sessions

The total duration of the 100 MUR sessions was 4796 minutes (80 hours) (Table 3.31).

Table 3.31: Duration of pharmacist-led sessions

Session	Procedures carried out	Total duration (minutes)	Number of sessions	Mean duration per session (minutes)	Range (minutes)	SD
MUR Session (t=0)	Semi-structured pre-intervention questionnaire	4796	100	48	35-69	7.16
	Medication reconciliation					
	INR testing					
	Development of pharmaceutical care plan					
	Counselling time					
Follow-up session (t=1)	Semi-structured post-intervention questionnaire	2434	99	25	17-35	4.42
	Assess implemented recommendations					
	Counselling time					

Ninety-five patients were satisfied with the duration of both clinical sessions. These patients 'agreed' or 'strongly agreed' that the pharmacist researcher spent sufficient time to discuss treatment needs.

3.13.2 Patient willingness to start using pharmacist-led medicine use review service

After attending the pharmacist-led MUR, 90 of the 99 patients attending the follow-up session 'agreed' or 'strongly agreed' that they would be willing to make use of the proposed service if the framework is implemented on a national level (Figure 3.27).

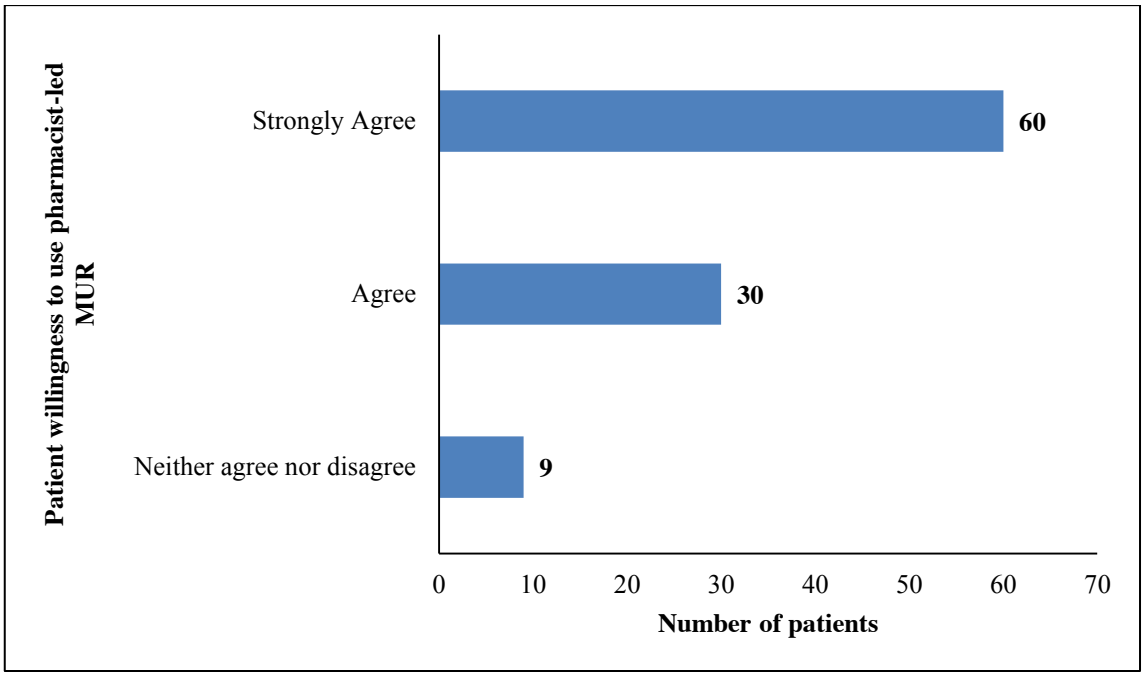


Figure 3.27: Patient willingness to start using pharmacist-led medicine use review service (n=99)

3.13.3 Perceived benefits of pharmacist intervention

Post-intervention, 90 of the 99 patients attending the follow-up session agreed that the pharmacist researcher's contribution in the management of anticoagulation changed their view on the community pharmacist's role and competencies and agreed that the community pharmacist can further expand responsibilities to respond to patient needs. Ninety-three of the 99 patients were satisfied with the anticoagulation education provided and they 'agreed' or 'strongly agreed' that after attending the clinical sessions their knowledge on anticoagulation treatment improved. Eighty-two patients 'agreed' or 'strongly agreed' that the printed material provided during the clinical session was beneficial. When stating the main benefits of the proposed MUR service, 54 patients stated that the MUR session improved their knowledge on anticoagulation (n=54) (Figure 3.28).

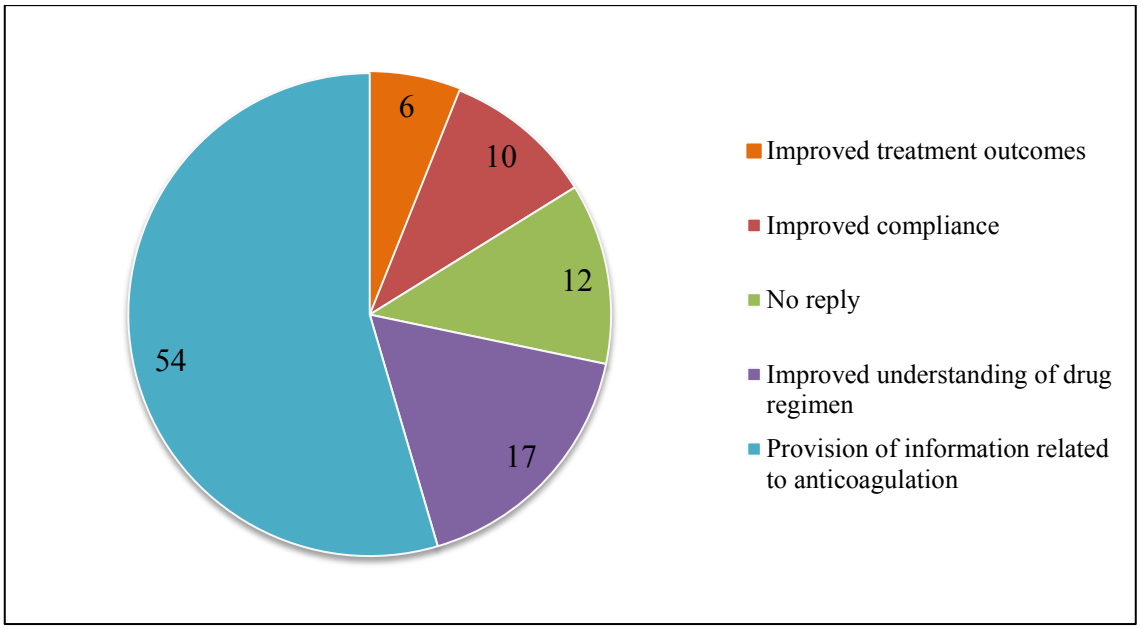


Figure 3.28: Patient perceptions on benefits of medicine use review service (n=99)

Chapter 4

Discussion

4.1 Impact of pharmacist-led medicine use review

Introduction of pharmacist-led anticoagulation medicine use review (MUR) clinics has the potential to improve warfarin utilisation by providing individualised patient care focusing on identifying and addressing drug-related problems (DRPs) (Roughead et al, 2011; Stafford et al, 2011). A targeted MUR is an advanced service where a pharmacist performs a comprehensive medication review to establish medication use, identify DRPs and develop an individualised medication profile and pharmaceutical care plan. This is the first study carried out in Malta to evaluate the impact of a community pharmacist-led MUR service for patients on warfarin and to explore ways community pharmacists can contribute in improving treatment outcomes and reducing anticoagulation-related complications. One hundred patients on warfarin were recruited to attend a targeted MUR session (pre-intervention) and were followed-up after two months (post-intervention) using a rigorous systematic approach.

To-date, most available literature related to pharmacist intervention in anticoagulation management focuses on INR control, warfarin dose management and provision of education (Chiquette et al, 1998; Dager et al, 2000; Burns et al, 2004; Rudd and Dier, 2010; Smythe, 2007; Shaw et al, 2011; Wong et al, 2011; Rossiter et al, 2013). There is limited literature that supports community-based MUR clinics targeting patients on anticoagulation therapy (Roughead et al, 2011; Stafford et al, 2011). Literature highlights benefits of pharmacist-led MUR with favourable therapeutic, safety and humanistic endpoints, including improvement in prescribing, patient knowledge, treatment adherence, quality of life, treatment outcomes and patient confidence in administering medications, and a reduction in the number of DRPs, polypharmacy, overuse or misuse of medications and medication costs (Berenguer et al, 2004; Youssef

et al, 2010; Castelino et al, 2010; Roughead et al, 2011; Avery et al, 2012; Blenkinsopp et al, 2012; Geurts et al, 2012; Hatah et al, 2014; Mossialos et al, 2015; Daba et al, 2016; Latif et al, 2016; Rodgers et al, 2016; Smith and Ferreri, 2016).

The DOCUMENT classification system allowed the pharmacist researcher to categorise and clearly describe each identified DRP. Use of the DOCUMENT classification system was found to be applicable in the present study setting. A total of 481 DRPs were identified in the MUR sessions. The patients assessed had a mean of 5 DRPs per patient, with 99% of the patients having at least 1 DRP identified. The high prevalence of DRPs identified, emphasised the need for provision of individualised patient assessment allowing for holistic consideration of patient health status. The result is comparable to other studies, where between 77% and 100% of patients assessed had at least 1 DRP identified (Sorensen et al, 2005; Pit et al, 2007; Krska and Avery, 2008; Castelino et al, 2010; Stafford, 2012; Guignard et al, 2015). The mean number of DRPs identified in various studies carried out in different countries and settings range from 1.3 to 8.6 DRPs per patient. The differences in the number of DRPs identified in these studies may be due to differences in the characteristics of the study population, severity of illness, prescribed medications, care setting and type of DRP classification system used (Table 4.1).

Table 4.1: Comparison of the number of drug-related problems identified in different studies

Reference	Country	Setting	Number and type of patients assessed	Mean number of DRPs identified per patient
Present study, 2017	Malta	Community pharmacy	100 patients on warfarin	4.8
Campbell et al, 2004	Chicago	Anticoagulation Clinic	327 patients on warfarin	6.1
Paulino et al, 2004	Austria, Demark, Germany, Netherlands, Portugal, Spain	Community pharmacy	435 patients discharged from hospital	5.9
Bell et al, 2006	Australia	Home medicine review	45 patients suffering from mental illness	8.2
Castelino et al, 2010	Australia	Home medicine review	224 patients >65 years	4.9
Kwint et al, 2011	Germany	Community pharmacy	118 patients using automated drug dispensing	8.6
Beckett et al, 2012	USA	Hospital	81 geriatric patients	1.4
Basheti et al, 2013	Jordan	Home medicine review	167 patients with chronic conditions	7.4
Lenander et al, 2014	Sweden	Primary care centre	209 patients with 5 or more medications	1.7
Tan et al, 2014	Australia	Hospital	82 patients with risk factors for DRPs	2.0
Guignard et al, 2015	Switzerland	Hospital	145 patients admitted to medical ward	2.7
Al-Jumali et al, 2016	Iraq	Hospital	1506 patients admitted to medical ward	1.3
Basheti et al, 2016	Jordan	Outpatient clinic	112 patients with chronic conditions	1.6
Geurts et al, 2016	Netherlands	Primary care centre	512 patients on cardiovascular drugs	2.2

The need for monitoring (30%), lack of compliance (20%) and need for patient education (19%) were the top DRPs identified in the present study. Consistent with findings in the present study, researchers in other studies identified a large percentage of DRPs related to need for monitoring, drug selection problems, such as drug interactions and issues with medication doses, need for patient education and need for improved compliance (Gilbert et al, 2002; Roughead et al, 2004; de Lyra et al, 2007; Aderounmu 2008; Gastelurrutia et al, 2011; Williams, 2013; Chan et al, 2014; Guignard et al, 2015; Al-Jumaili et al, 2016; Basheti et al, 2016; Hsu et al, 2016).

Medications reported to be associated with a large number of DRPs include cardiovascular, central nervous system, respiratory and anti-infective drugs (Rogers et al, 1994; Roughead et al, 2004; Hammerlein et al, 2007; Kryska and Avery 2008; Pit et al, 2009; Stafford, 2012; Williams, 2013). With respect to cardiovascular drugs, warfarin is associated with a high rate of DRPs (Campbell et al, 2004; Stafford et al, 2011; Stafford, 2012; Boswell and Bungard, 2015; Daba et al, 2016; Hsu et al, 2016).

Ninety percent of patients in the present study had at least 1 warfarin-related DRP, with a mean of 2 warfarin-related DRPs per patient. Similarly, a study in Australia reported that 86.4% of the study population had at least 1 warfarin-related DRP, with a mean of 1.4 warfarin-related DRPs per patient (Stafford et al, 2011). A retrospective study carried out in an anticoagulation clinic in Chicago, USA, reported that over a seven month period, a mean of 4.5 warfarin-related DRPs per patient were identified (Campbell et al, 2004).

The top warfarin-related DRP categories identified in the present study were the need for education reinforcement to improve patient knowledge and compliance, followed by drug selection problems. The identified warfarin-related DRPs are comparable to warfarin-related DRPs identified by Campbell et al (2004) in the UK and Stafford et al (2011, 2012) in Australia.

Patients on warfarin attend anticoagulation clinics frequently for INR monitoring. Guidelines suggest a maximum interval of twelve weeks between INR tests in patients who are well-stabilised on warfarin (Wigle et al, 2013). The high proportion of DRPs identified could imply that although patients attend for routine INR testing, DRPs may be overlooked since the focus of health professionals at anticoagulation clinics is to sustain target INR with no dedicated consultation to assess and review patient progress carried out (Boswell and Bungard, 2015).

Inclusion of a pharmacist-led MUR service provides the opportunity to address DRPs related to medication management beyond INR control and to facilitate prevention of DRPs. Pharmacists managing anticoagulation MUR clinics should extend their focus to identify clinical issues which are not only related to anticoagulation therapy (Boswell and Bungard, 2015). Sixty percent of identified DRPs in the present study were not warfarin-related, demonstrating that individualised comprehensive patient assessment must ensure that patient-centered care delivery is not limited to anticoagulation therapy.

Risk of adverse anticoagulation-related clinical outcomes, such as risk of bleeding, stroke, myocardial infarction, vascular events and mortality increase with increasing number of concomitant medications prescribed with warfarin (Focks et al, 2016; Piccini

et al, 2016). Polypharmacy and polymorbidity were evident in the study population, where on average, each patient suffered from 3 comorbidities and was prescribed 6 chronic medications. A statistically significant relationship between the number of DRPs identified and the number of medications prescribed, the number of comorbidities and older age was observed ($p<0.05$). Patients with frequent changes in treatment and on multiple drug therapies have a higher probability of experiencing DRPs (Hajjar et al, 2007; Aderounmu, 2008; Kaur et al, 2012; Ahmad et al, 2014; Blozik et al, 2013; Messerli et al, 2016). Polypharmacy increases the risk of drug-drug interactions (DDIs), adverse drug reactions(ADRs) and may lead to reduction in adherence to treatment and quality of life (Teklay et al, 2014; Wang et al, 2015; Abdel Aziz et al, 2016; Focks et al, 2016; Messerli et al, 2016; Piccini et al, 2016). A statistically significant relationship ($p<0.05$) between the number of medications prescribed and the number of DDIs was observed.

Cognitive decline and the number of comorbidities increase in elderly patients, hence increasing the risk of polypharmacy, susceptibility to DRPs and difficulty in understanding and appropriately managing medications (Newall et al, 2005; Chan et al, 2012; Nasser et al, 2012; Williams, 2013; Shrestha et al, 2015; Dowling et al, 2016, Dowden, 2017). Similarly to other studies (Miura et al, 2009; Virjo et al, 2010, Gallagher et al, 2014; Bjorck et al, 2016), the mean age of the patients in the present study (70.5 years) suggests that warfarin is predominantly prescribed in the older population. Frequent laboratory and non-laboratory monitoring is required in elderly patients and patients with polypharmacy to assess the safety and efficacy of medications (Handler et al, 2008).

Strategies to minimise occurrence of polypharmacy contribute to reducing warfarin-related complications (Picinni et al, 2016; Proietti et al, 2016). Pharmacist-led MUR allows identification of medications that may be unnecessary or which negatively impact treatment outcomes. Recommendations by the pharmacist researcher following the MUR sessions resulted in 30 drug discontinuations and 21 dose reductions, decreasing the number of prescribed medications by 2.1%. Reduction in polypharmacy post-MUR was similarly observed in other studies (Blenkinsopp et al, 2012; Mancini and Clifford, 2013; Lenander et al, 2014, Manfrin et al, 2015).

Improvement in patient knowledge on anticoagulation improves INR control and reduces serious ADRs (Stafford et al, 2011). MUR sessions improve patient knowledge and adherence (Clark et al, 1972; Wyness, 1990; Newall et al, 2005; Blenkinsopp et al, 2012). The mean score (7 out of 12) obtained in the pre-intervention warfarin knowledge test indicates that patients had poor understanding of anticoagulation therapy before the pharmacist intervention, which is consistent with other studies reporting poor patient understanding of warfarin treatment and lack of awareness of factors affecting the mechanism of action of warfarin (Tang et al, 2003; Davis et al, 2005; Hu et al 2006; Smith et al, 2010; Winans et al, 2010; Baker et al, 2011; Shrestha et al, 2015; Obamiro et al, 2016). Pre-intervention, only 25% of patients in the present study obtained a pass score (9 out of 12) in the warfarin knowledge test, which is comparable to other studies reporting adequate anticoagulation knowledge in 5.8% to 39% of patients (Davis et al, 2005; Hu et al 2006; Baker et al, 2011; Shrestha et al, 2015). A significant association ($p<0.05$) between the pre-intervention warfarin knowledge score and age was observed in the present study, with various studies confirming that age has a negative effect on

patient anticoagulation knowledge (Tang et al, 2003; Wilson et al, 2003; Hu et al, 2006; Sayeed et al, 2012; Jenzarli et al, 2013; Wang et al, 2014; Shrestha et al, 2015).

The main knowledge deficits observed in the present study, similarly to the educational gaps identified in other studies, were related to warfarin interactions, significance of high and low INR values, possible consequences of under and over anticoagulation and management of missed doses (Taylor et al, 1994; Lane et al, 2006; Roche et al, 2003; Yahaya et al, 2009; Khudair et al, 2010; Smith et al, 2010; Van Damme et al, 2011; Nasser et al, 2012; Jenzarli et al, 2013; Wang et al, 2014). During the MUR session, the pharmacist researcher addressed educational gaps by providing verbal and written counselling.

Face-to-face intervention improves communication and allows health professionals to provide targeted education according to a patient's individual needs (Nasser et al, 2012; Wang et al, 2014). Use of verbal communication alone often fails to result in effective patient counselling since patients sometimes misunderstand or forget the points discussed. Providing effective written information supplementing oral communication is vital to ensure patient-centred care that reinforces and improves patient education and compliance (Renuka and Pushpanjali, 2013).

Post-pharmacist intervention an improvement in the knowledge test score was observed in 91% of the patients. The percentage of patients who achieved a pass score following pharmacist intervention increased from 25% to 68%. A statistically significant improvement ($p<0.05$) in the mean knowledge score obtained in the warfarin knowledge test post-intervention was observed, indicating that pharmacist intervention

was effective in improving anticoagulation knowledge. Similarly in other studies, statistically significant improvements in patient anticoagulation knowledge after pharmacist intervention were observed (Krittathanmakul et al, 2006; Khudair et al, 2012; Winans et al, 2010; Eisa, 2013; Jenzarli et al, 2013; Collins et al, 2014). A statistical significant ($p<0.05$) inverse relationship between improvement in warfarin knowledge test score and age was observed in the present study indicating that after a single MUR session, older patients did not improve their anticoagulation knowledge to the same level as younger patients.

Since not all patients obtained a pass score in the warfarin knowledge test, this points out that a single MUR session was not sufficient and ongoing follow-up sessions may be needed. Lack of adequate and repetitive counselling contributes to decline in patients' knowledge (Webber, 1990; Hu et al 2006; Collins et al, 2014; Shrestha et al, 2015). In a study performed in Ireland by Collins et al (2014) a higher mean score in the warfarin knowledge test was observed 24 hours after pharmacist intervention. When assessed 28 to 56 days post-pharmacist intervention, a statistical deterioration in mean knowledge score was observed, although the mean score obtained was still higher than the mean score obtained pre-pharmacist intervention (Collins et al, 2014). A study performed in Australia by Roughead et al (2011), suggested the need for a six-monthly review by a pharmacist for patients taking warfarin to allow ongoing educational interventions and treatment management strategies since educational impact is time-dependent and may be lost after a few months.

No significant association ($p>0.05$) between duration of warfarin use and warfarin knowledge test score was observed. Literature presents conflicting evidence on the

effect of treatment duration and patient knowledge on anticoagulation. Smith et al (2010) and Hasan et al (2011) report no association between the duration of warfarin treatment and patient knowledge. However, Tang et al (2003), Jenzarli et al (2013) and Shrestha et al (2015) confirm a positive relationship between treatment duration and knowledge. The assumption that knowledge improves with treatment duration may arise since patients having experience with treatment management have more opportunities to expand their knowledge and this hypothesis may lead to lack of counselling in patients who are established on treatment (Jenzarli et al, 2013).

The MUR service is beneficial for patients who have been newly prescribed warfarin as well as for patients who have been managed on warfarin for a long period, as a means of ongoing counselling and continuous reinforcement. Pharmacist-led MURs may be considered as an opportunity for continuous provision of patient education (Roughead et al, 2011; Blenkinsopp et al, 2012).

Poor patient education and inadequate accessibility to information encourage development of structured MURs incorporating educational programmes (Tang et al, 2003; Jones and Lacombe, 2009; Nasser et al, 2012). Only 25% of the patients in the present study were provided with counselling on warfarin therapy at the time of initial prescription. Patients claimed that they were not satisfied with the current level of anticoagulation education provided at the government health centres. The main reason for lack of counselling and provision of sufficient advice is time constraints due to large workloads. Other studies similarly report that patients on warfarin are not provided with sufficient clear advice or adequate treatment information (Taylor et al, 1994; Kagansky et al, 2004; Azzopardi. 2010; Nessar et al, 2012; Jenzarli et al, 2013; Mifsud, 2013).

Improved patient knowledge is associated with improved adherence to warfarin therapy (Kim et al, 2011; Wang et al, 2014; Ababneh et al, 2016). Medication adherence is a modifiable factor, hence patient support and interventions to enhance adherence by the community pharmacist may result in improved treatment outcomes (Clifford et al, 2010; Brown et al, 2012; Ababneh et al, 2016). Pre-intervention, 25% of the patients reported missing at least one warfarin dose in the two weeks prior to the MUR session. Similar non-adherence rates were estimated in international studies, where between 21% and 40% of the patients skipped at least one warfarin dose (Parker et al, 2007; Kimmel et al, 2008; Platt et al, 2008; Smith et al, 2010; Amara et al, 2016). Post-pharmacist intervention, the non-adherence rate reduced significantly from 25% to 11%, hence the pharmacist intervention was effective in improving adherence to warfarin ($p<0.05$). Patients who were found to be non-adherent to warfarin during the MUR session were advised on the risks of non-adherence and on the use of compliance aids to improve adherence, namely the warfarin dosing calendar in the developed 'Anticoagulation and Medication Profile' and pill organisers. Nineteen of the 25 patients who missed at least one dose prior to the MUR session were adherent to warfarin in the follow-up session with implementation of compliance aids. In a study by Nochowitz et al (2009), the use of a monthly medication organiser led to improvement in warfarin adherence and the time spent in therapeutic range.

Poor adherence to warfarin was reported to be associated with younger age, male gender and poor cognitive function (Kneeland and Fang, 2010). In the present study it was observed that males and elderly patients had lower warfarin adherence rates. In a study by Fang et al (2006) it was observed that limited health literacy was significantly

associated with poor anticoagulation knowledge, however not significantly associated with non-adherence. Adherence is a behavioural process, which is affected by patient knowledge, motivation and skills to undertake recommended behaviour (Miller et al, 1997; Pamboukian et al, 2008; Ababneh et al, 2016). In the present study no significant association between patient knowledge pre-intervention and level of adherence was observed.

An important factor in ensuring INR control is administration of the correct warfarin dose, since incorrect warfarin dosing may lead to increased mortality risk [19](Kimmel et al, 2008). During the MUR session the pharmacist researcher identified 4 cases of incorrect warfarin dosing which could have led to treatment complications; 3 patients were administering a different warfarin dose to the prescribed dose and another patient was given a prescription with an incorrect warfarin dose not concordant with the dose written on the yellow anticoagulation booklet. Post-intervention, all patients were administering the correct warfarin dose.

Adherence to warfarin treatment is not only dependent on the number of missed doses (Kim et al, 2011). A warfarin adherence score was used to measure and monitor how factors affecting INR control are managed by the patient. Pre-intervention, 51.5 % of patients obtained a score of 1 or higher, indicating that more than half of the patients had an issue related to compliance which needed improvement. The top issues identified were skipping the warfarin dose and variable consumption of alcohol and Vitamin K-containing foods. Post-intervention, only 18.6% of patients obtained a score of 1 or

[19] Rommelfanger J. Incorrect warfarin dosage fatal at Philadelphia hospital. Medscape [Internet]. 2001 [cited 2017 May 05]. Available from: http://www.medscape.com/viewarticle/783343.

higher. A significant decrease in adherence score was observed showing an overall improvement in patient adherence post-pharmacist intervention ($p<0.05$).

Anticoagulation therapy is associated with various inconveniences restricting the social lifestyle of patients due to the need for regular INR monitoring, continuous threat of complications and risk of DDIs (Lancaster et al, 1991; Dantas et al, 2004; Buhagiar, 2007; Das et al, 2007; Das et al, 2009; Prins et al, 2009; Kneeland and Fang et al, 2010). Similarly, a negative perception on the effect of warfarin on a patient's quality of life was observed in the present study, with patients stating that warfarin dose adjustments complicate treatment. A significant improvement in patient perception regarding quality of life was observed post-pharmacist intervention ($p<0.05$), suggesting that the counselling session in the MUR improved patient understanding and simplified treatment management.

Improved patient knowledge, warfarin adherence and patient satisfaction with treatment improves INR control[20] (Beyth et al 2000; Tang et al in 2003; Kaganskey et al, 2004; Kimmel et al, 2008; Stafford et al 2011; Nasser et al, 2012; Clarkesmith et al, 2013; Wang et al, 2014; Shrestha et al, 2015). Pharmacist intervention in the present study resulted in a significant increase in the percentage time spent WTR ($p<0.05$). Maximising time spent WTR improves treatment outcomes, while lack of INR control leads to increased risk of treatment complications (Ansell et al, 2001; Ryan et al, 2008; Melamed et al, 2011). A patient's target INR range is dependent on the indication of

[20] Eltayeb TYM, Mohamed MS, Elbur AI, Elsayed ASA. Satisfaction with and adherence to warfarin treatment: A cross-sectional study among Sudanese patients. J Saudi Heart Assoc [Internet]. 2016 [cited 2017 May 8]. Available from: http://www.journalofthesaudiheart.com/article/S1016-7315(16)30162-2/fulltext.

warfarin and on the clinical situation of the patient (Keeling et al, 2011). Sixty-one percent of the study population had an INR target range between 2.0 and 3.0. A systematic review and meta-analysis by Oake et al (2008), confirmed that a target range between 2.0 and 3.0 is the safest, since the risk of haemorrhage increases when INR values exceed 3.0 and the risk of thromboembolism increases when INR values are less than 2.0. The British Committee for Standards in Haematology guidelines suggest that for maximum benefits of warfarin the TTR should be 60% or more (Baglin et al, 2006, Keeling et al, 2011, Shaw et al 2011). The number of patients in the present study with a TTR of 60% or more increased from 49 to 59, post-intervention. During the MUR session, POCT INR testing was carried out and 40% of the patients were found to have an INR outside their target range. These results confirm the need for targeted MUR services focusing on anticoagulation management to improve INR control by screening for DRPs, assessing treatment and identifying confounding factors causing fluctuations in INR.

Daba et al (2016) highlighted the importance of screening patients on warfarin for DRPs to ensure treatment effectiveness and to prevent ADRs. The authors identified sub-therapeutic doses, over-therapeutic doses and potential DDIs as the most frequent DRPs in patients on warfarin (Daba et al, 2016). In the present study, DDIs was the third most common DRP subcategory identified (13.1%). Warfarin has a large number of possible DDIs, hence appropriate treatment selection of concomitant medication and continuous close monitoring is important to minimise complications and ensure treatment safety (Wittkowsky et al, 2004; Anderson et al, 2005; Hallas et al, 2006; Douketis et al, 2007; Suh et al, 2012).

Following screening of DRPs, clinical intervention recommendations are required to improve treatment outcomes. Almost all patients (99%) attending the MUR session received one or more clinical intervention recommendation, with a mean of 5 recommendations per patient. Ninety-seven percent of the clinical intervention recommendations were classified as having the potential to improve patient care. The top recommendations were provision of information (38%), need for monitoring (31%) and physician referral required (30%). The recommendations were directed towards the physician, patient or community pharmacist. Clinical issues requiring provision of information were addressed by the pharmacist researcher through patient education and counselling. Forty-nine percent of the recommendations were directed for consideration by the physician, which is comparable to the 52% of DRPs referred for physician attention by Basheti et al (2016) in Jordan. Recommendations referred to the physician included interventions to assess treatment selection or dosage, need for change in treatment or need for monitoring. Interventions that required provision of DAAs were referred for community pharmacist intervention. Recommendations directed to the patient were related to non-laboratory monitoring and treatment adherence.

A positive collaboration between the pharmacist, physician and patient is necessary for the provision of optimal pharmaceutical care (Geurts et al, 2013). MUR services increase community pharmacist contribution in primary care. Pharmacist offering clinical services must be able to participate in multidisciplinary teams and collaborate with other health professionals to enable delivery of quality care with effective use of all resources (Rigby, 2010; Claeys et al, 2013).

A high implementation rate of the pharmacist researcher's recommendations (84%) was observed, indicating the positive value of the pharmacist-led MUR. Similar acceptance rates which range from 54% to 92% were observed in other studies (Sorensen et al, 2004; Beckett et al, 2012; Fernandez-Llamazares et al, 2012; Stafford, 2012; Tan et al, 2014; Guignard et al, 2015; Basheti et al, 2016). In the present study clinical recommendations associated with 'monitoring' (98.6%), 'compliance' (93.8%), 'toxicity and adverse drug reactions' (89.5%) and 'education and information' (93.8%) had a higher implementation rate compared to recommendations associated with 'undertreated' (57.2%), 'over or under dose' (54.5%) and 'not classifiable' (17.6%).

Studies report a physician acceptance rate of clinical interventions recommendations by pharmacist ranging between 41% and 96% (Krska et al, 2001; O'Dell et al, 2005; Kucukarslan et al, 2003; Galindo et al, 2003; Sellors et al, 2003; Sorensen et al, 2004; Doucette et al, 2005; Patel et al, 2005; Viktil and Blix, 2008; Basheti et al, 2016). The high physician acceptance rate (83%) of the pharmacist researcher recommendations indicates that the physicians involved acknowledged the pharmacist's input.

Written recommendations on the developed 'Anticoagulation and Medication Profile' were used to communicate the pharmacist researcher's recommendations with the physician. Twenty-one of the 40 unresolved issues referred for physician attention were never communicated to the physician. Rejected recommendations by physicians were related to dose changes and need to start or stop a particular treatment. Studies show that a pro-active approach through verbal notifications and health-care team discussions result in higher acceptance rates of pharmacist recommendations compared to written reactive notifications (Doucette et al, 2005; Patel et al, 2005; Viktil and Blix, 2008).

Eighty-two percent of the DRPs classified in 'not classifiable' category remained unsolved. These DRPs, were related to smoking cessation, reduction in alcohol binging and diet modifications. The pharmacist researcher's recommendations and counselling did not elicit a change in patient behaviour since most patients were not ready to stop the habit or change their lifestyle. The pharmacist should possess coaching skills, be assertive and confident in providing advice which will help patients to modify current behaviours (Petty and Fortini, 2016). Studies obtaining a successful rate of smoking cessation following pharmacist intervention offered programme-based behavioural and motivational counselling with the support of pharmacotherapy and frequent follow-up sessions (Hudmon et al, 2003; Su et al, 2012; Fai et al, 2016). Addictions cannot be solved simply by patient counselling on the importance of lifestyle changes, focused motivational interviewing directed towards stimulating a patient's desire to modify lifestyle is necessary (Rollnick and Miller, 1995; Stewart and Fox, 2011; Hardcastle et al, 2015).

Regular MUR sessions allow the pharmacist to gain the patient's trust, for continuous motivational interviewing, provision of education, goal setting and action planning to help the patient to engage in health behaviour changes. MUR provides face-to-face individualised consultations, where the patient is given the opportunity to build a professional relationship with the health provider, allowing two-way communication and encouraging active participation in treatment decisions (Latif et al, 2011; Sheridan et al, 2012). As part of the MUR service, pharmacists may educate patients about alternative treatments. Eleven patients requested education on NOACs during the MUR session, where patients were encouraged to discuss alternative anticoagulation options with the physician. Two patients switched to NOACs following pharmacist intervention

and discussion with the physician. Provision of regular MUR improves accessibility to information and advice regarding medication use (Blenkinsopp et al, 2007).

The significant number of DRPs identified and the proportion of unsolved DRPs confirm that continuous follow-up MUR sessions are required to ensure that the positive impact of pharmacist intervention and continuity of care is maintained. In the study by Roughead et al (2011) the positive effect following MUR, which resulted in a 79% reduction in hospitalisation rate of warfarin patients due to bleeding, was lost after six months, indicating that the effect of MUR is time-dependent and MUR follow-up every six months was suggested. In the UK, MUR sessions are carried out once yearly, with the General Medical Service contract specifying that patients on chronic medications should have MUR performed every fifteen months and repeated before if there are changes in treatment (Blenkinsopp et al, 2012). In 2001, the National Framework for Older People Directive in the UK stated that patients over the age of 75 years should have annual MUR, while patients taking more than 4 medications should have a MUR every six months with the aim to reduce treatment complications[21].

Various studies reported reduction in the number of emergency hospital visits, overall health costs and hospital days due to MUR, however there is conflicting evidence about the effect of MURs on the reduction of hospital admissions and mortality (Ellis et al, 1992; Galt, 1998; Bond et al, 2000; Nazareth et al, 2001; Bunting and Cranor, 2003; Cranor et al, 2003; Holland et al, 2005; Pacini et al, 2007; Lenaghan et al, 2007; Krska

[21] Department of Health. National service framework for older people [Internet]. UK: GOV.UK; 2001 [cited 2017 April 30]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/198033/National_Service_Framework_for_Older_People.pdf

and Avery, 2008; Holland et al, 2008; Roughead et al, 2011; Blenkinsopp et al, 2012; Geurts et al, 2012).

In 2007, Lenaghan et al, observed no positive impact of MURs on clinical outcomes to patients over 80 years, with researchers suggesting a shift in focus of MUR services from elderly patients to at-risk populations. Existing literature demonstrates that targeted MUR interventions for patients with complex treatments, with poorly-controlled conditions or following hospital discharge are more effective than MUR for elderly patients (Zermansky et al, 2006; Holland et al, 2008; Nkansah et al, 2010; Ahmad et al, 2014; Kolhatkar et al, 2016). MUR should be offered to patients at high risk for DRPs, including patients with polypharmacy, high-risk medications, significant changes to treatment and insufficient response to drug therapy[22] (Messerli et al, 2016). The need for provision of MUR to patients on warfarin was established in the present study since a large number of DRPs were identified, confirming that patients require close assessment and will benefit from regular MUR sessions. An internal audit performed between the 2010 and 2013 in Southeast Essex in the UK, among patients receiving anticoagulants, identified that 80% of the population studied required appropriate treatment review to optimise anticoagulation therapy. These findings highlighted the need for improvement in anticoagulation management and led to the development of an Anticoagulation Review Clinic, targeting patients with a TTR below 65% to improve anticoagulation management (Dowling et al, 2016).

[22] NHS Cumbria Medicines Management Team. Clinical medication review. A practice guide. [Internet]. UK: NHS Cumbria; 2013 [cited 2017 April 30]. Available from: URL: http://www.cumbria.nhs.uk/ProfessionalZone/MedicinesManagement/Guidelines/MedicationReview-PracticeGuide2011.pdf

Few studies to assess the outcomes of community pharmacist-led MUR focusing on anticoagulation treatment have been performed (Amuroso, 2004; Roughead et al, 2011; Stafford et al, 2011). Dager et al (2000) and Wong et al (2011) confirmed that an inpatient pharmacist-managed anticoagulation service improved anticoagulation outcomes, TTR, coordinated patient transfer and reduced costs and readmissions. In an outpatient setting, Poon et al (2007) observed no difference in INR control between patients in the pharmacist intervention and control group. Amuroso (2004) confirmed that a community pharmacist-led anticoagulation clinic increased in-range INR and reduced ADRs and Garwood et al (2014) concluded that a specialised pharmacist-led anticoagulation clinic provided safe and effective treatment. Roughead et al (2011) reported that an advanced pharmacist-led MUR service providing ongoing patient education and warfarin management strategies delays time for warfarin-related hospitalisation.

Expansion of the pharmacist's role with the provision MUR may be associated with non-acceptance of both physicians and patients due to lack of experience and familiarisation with the MUR service (Bryant et al, 2009; Youssef et al, 2010; Rieck and Pettigre, 2013; Smith and Ferrari, 2016). Patients who experienced pharmacist-led MURs reported several benefits, including improvement in knowledge on general medicine, increased understanding of the purpose of and need for medications and reassurance on concerns related to treatment (Carter et al, 2013). Physicians and patients familiar with pharmacist-led MURs recognise the great potential of the service which may lead to increased quality of care and safety of treatment (Coleman et al, 2001; Bissell et al, 2008; Carter et al, 2012; Maracle et al, 2012; Shah et al, 2013).

Patients associate pharmacist-led anticoagulation clinics with reduced warfarin-related DRPs and treatment complications (Nau et al, 2000).

Patients in the present study were unaccustomed to the availability of pharmacist-led services and the possibility of expanding the community pharmacist's role to offer MUR and warfarin dosing. Following the MUR session, a high level of patient satisfaction was observed. Almost all patients (99%) returned for the follow-up session, confirming that patients were comfortable with the service. Patients stated that potential benefits of the enhanced pharmacist-led service were provision of knowledge and improved compliance, understanding of anticoagulation treatment, patient confidence regarding medication management and treatment outcomes. Ninety-one percent of the patients expressed willingness to start using the MUR service if it is implemented in Malta.

Following the MUR session, all patients expressed satisfaction with the pharmacist's input and viewed the pharmacist as a knowledgeable health professional who can provide specialised one-to-one interventions to contribute to improved treatment outcomes. A similar level of patient satisfaction was reported in other studies[23] (Latif et al, 2011; Sheridan et al, 2012; Manfrin et al, 2015; Dowling et al, 2016). Patient satisfaction with MUR service is important for successful implementation of the service since it ensures sustainability, effective utilisation and positive health outcomes. Satisfied patients will be more willing to re-attend for a MUR session (Naik Panvelkar et al, 2009; Carter et al, 2013). In an Italian study, 75% of patients stated that they

[23]University of Reading. The Medicines Use Review: Patient satisfaction survey [Internet]. UK; 2016 [cited 2017 May 05]. Available from: http://www.reading.ac.uk/web/files/mur-summary-v2.pdf

benefitted from the MUR service, 50% were interested in having another MUR session and 85% were willing to recommend MUR to other patients (Manfrin et al, 2015).

Patients worried about their medications and aware of the benefits related to MUR are usually more willing to use the service (Carter et al, 2013). Patient willingness to re-attend for MUR is influenced by listening skills, friendliness and empathy of the pharmacist providing the service, hence the pharmacist must ensure excellent interpersonal communication skills (Naik Panvelkar et al, 2010; Shipley, 2010; Carter et al, 2015).

POC INR testing devices allow for patient-centered INR testing since they provide the opportunity for instant result interpretation, immediate dosing advice and individualised counselling (McBane et al, 2005; Lippi et al, 2008; Thompson et al, 2009). Prior to the introduction of POC INR testing in Malta in 2014, patients trusted and felt more comfortable with laboratory-based INR testing (Mifsud, 2013). A change in patient perception was observed in the present study with patients who already switched to POC INR testing confirming that finger-prick testing and direct interaction with the health professional providing dosing instructions during the consultation rather than receiving the dose by telephone or postal mail was the preferred method. Patient satisfaction with the POCT service encourages further developments so that more patients can benefit from POCT and related services.

Use of POCT devices and dosing algorithms can assist pharmacists in selecting the appropriate warfarin dose (Dawson et al, 2012; Rossiter et al, 2013; Downing et al, 2016). To-date, Maltese legislative requirements do not permit warfarin dosing

adjustments to be carried out by a pharmacist. Pre-intervention, only a minority of the patients expressed feeling comfortable with the pharmacist having responsibility for warfarin dose adjustments. The number of patients in agreement that the pharmacist is competent to perform warfarin dose changes increased significantly post-intervention ($p<0.05$). Algorithm-based dosing decisions improve the quality of anticoagulation control and can be easily integrated into routine practice (Meijer et al, 2011). Various studies have reported that pharmacist dosing using standard algorithms resulted in reduced dosing errors, improved treatment outcomes and enhanced patient care (Dager et al, 2000; Boddy, 2001; Burns, 2004; Wong et al, 2011; Dawson, 2012; Downing et al, 2016).

Use of pharmacogenomics testing to individualise warfarin dosing as opposed to trial and error dosing can improve determination of initial warfarin doses, since genes may influence warfarin metabolism and sensitivity and are associated with patient response to warfarin[24,25] (Kamali and Wynne, 2010; Marcetto et al, 2016; Johnson et al, 2017). In a local study by Attard (2008), 38% of the Maltese population were found to carry a variant allele that contributes to a reduction in warfarin metabolism hence these patients would require lower warfarin doses. Pirmohamed et al (2013) concluded that use of genotype-guided warfarin dosing using a POCT genotype assay for CYP2C9*2, CYP2C9*3 and VKORC1 achieved superior INR control compared to standard dosing during initiation of warfarin. Availability of POCT genotyping devices may allow the

[24] Institute of Medicine (US) Roundtable on Translating Genomic-Based Research for Health. The Value of Genetic and Genomic Technologies: Workshop Summary. Pharmacogenomic testing to guide warfarin dosing [Internet]. Washington: National Academies Press (US); 2010 [cited 2017 May 05]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK52750/.

[25] American College of Cardiology. "Genetically guided warfarin dosing lowers risk of some adverse events." ScienceDaily [Internet]. 2017 [cited 2017 April 30]. Available from: www.sciencedaily.com/releases/2017/03/170320091104.htm.

introduction of pharmacist-led genotyping as part of the community pharmacist-led MUR service to individualise warfarin therapy.

In Malta, to-date there is no pharmacist input in anticoagulation management. Inclusion of a pharmacist in anticoagulation management with the possibility of offering MUR services will provide a holistic patient-focused service with individualised consultation with the intention to improve anticoagulation control. Community pharmacists must embrace new practising trends and assume more active and direct involvement in patient care which may create various innovative opportunities (Dobson et al, 2009). Studies confirm that pharmacists should be more enthusiastic about their potential to offer innovative services to support patients in therapy management. Willingness of community pharmacists to expand their services is reported to be a barrier to development of a patient-centered clinical service in community, with main concerns reported including level of knowledge and confidence to provide a specialised service, increased responsibility, higher workload and need for reimbursement for the service provided (Bryant et al, 2009; Rieck and Pettigre, 2013). Other barriers that may limit pharmacist willingness to expand clinical roles include lack of practical skills, inadequate access to accurate patient data and non-availability of clinical guidelines and regulations (van Mil et al, 2001; Sanchez and de las Mercedes, 2013; Mehralian et al, 2014). Lack of motivation from pharmacists was observed in studies performed in Malta with participating pharmacists not willing to offer an anticoagulation service and adjust warfarin doses (Buhagiar, 2007; Azzopardi, 2010).

MUR formalises the counselling role of pharmacists, enhances pharmacist professional status and presents an opportunity for pharmacists to be involved in patient medication

management (McDonald et al, 2010; Latif et al, 2011). Pharmacists offering anticoagulation services must ensure adequate competence and confidence in offering counselling on anticoagulation treatment. Accreditation programs for pharmacists providing MUR services will certify that pharmacists have adequate clinical and pharmaceutical knowledge, are able to access and evaluate patient medical information, document recommendations, contribute to safe and effective medication management and possess necessary skills including communication, rapport building, time management, leadership, teamwork and decision-making skills (Dugan, 2006; Latif et al, 2011; Manfrin et al, 2015). MUR may lead to development of other professional pharmacy services and provide community pharmacists with greater opportunities to be involved in patient medication management. Possible services include provision of DAAs, home medicines review and pharmacist prescribing.[26]

Participation of community pharmacists in patient medication management through the provision of MURs contributes to seamless pharmaceutical care (Nickerson et al, 2005). In Malta, the healthcare system is still fragmented and lacks sufficient seamless care which does not allow accurate transfer of patient information from one health care setting to another since there are no standard procedures for medication reconciliation. Studies confirm that pharmacists are able to compile medical histories and manage patient medications efficiently (Gurwich, 1983; Nester and Hale, 2002; Cranor et al, 2003; Beckett et al, 2012; Tan et al, 2014). The developed 'Anticoagulation and Medication profile' (Appendix 2) was found to be an efficient way to perform medication reconciliation. The profile was used as a tool to reduce medication errors,

[26] Moffitt K, Wassef C. Specialist roles in pharmacy. Pharm J [Internet]. 2014 [cited 2017 May 05]. Available from: http://www.pharmaceutical-journal.com/publications/tomorrows-pharmacist/specialist-roles-in-pharmacy/11135403.article

identify drug discrepancies, improve patient care and as a means of communication between health professionals to collaborate and develop treatment plans.

The 'Anticoagulation and Medication profile' (Appendix 2) may be further developed to be used as an official patient medical record, where each health professional documents interventions, recommendations or changes in treatment. Such a documentation system may improve provision of seamless care. Further advancements may lead to introduction of electronic patient health records as systematised collection of all patient medical history in digital format that can be accessed by various health professionals across the health sector. Improving availability of a patient's medical history may positively influence treatment management and prescribing (Manca, 2015).

The present study has established that the 'Warfarin Knowledge Test' and 'Adherence Score' used, provided valuable information on patient knowledge and adherence to treatment. Use of similar scores to assess patient's anticoagulation knowledge and to measure the patient adherence by assessing variables affecting INR control is a relatively new concept. In Malta, no established methods are currently used in practice. Both tools are effective, feasible and practical to use and allow patient assessment over a period of time.

Further development of knowledge scores, adherence scores and medication reconciliation tools may lead to implementation of standardised methods to perform MURs, assess patient knowledge and adherence with the aim to improve overall therapy management and assist the healthcare provider to design an individualised treatment plan. Appropriate regulations and contractual frameworks are essential for formalisation

of MUR services. Development of a framework, regulations and policies, will stimulate implementation and align roles and objectives for delivery of coordinated care by pharmacists (Mehralian et al, 2014).

Designing a system based on national guidelines and standardised documents will safeguard consistency, transparency and maintenance of high standards (Claeys et al, 2013). Various strategies will be required to ensure successful and sustainable service provision following implementation. The framework will outline comprehensive guidelines, appropriate standard operating procedures, methods for quality control and quality assurance of the service, standard pharmacist training and accreditation processes. Strategies to encourage patient and pharmacist enthusiasm to participate, evaluate service outcomes and enhance professional relationship between physicians and pharmacists to improve communication are required.

Results from Mifsud et al (2013) and from the present study may be used as the fundamental basis on which a service protocol will be designed and set-up, to ensure provision of a pharmacist-led professional monitoring and MUR service for patients on warfarin. Mifsud et al (2013) reported that the introduction of a national community pharmacist-led anticoagulation monitoring service for patients stabilised on warfarin will improve current anticoagulation management by reducing fragmented care and improving INR testing accessibility, patient satisfaction, clinical reliability and therapeutic effectiveness.

The positive outcomes observed following the pharmacist-led MUR session in the present study encourage the set-up of an 'Anticoagulation Review Clinic' to where patients on warfarin will be referred for regular community pharmacist-led MUR. The

first MUR session is to be performed following treatment initiation and pharmacist participation in anticoagulation management should improve treatment efficacy and minimise ADRs. Establishment of an Anticoagulation Review Clinic will enhance collaboration between physicians and community pharmacists and encourage seamless care.

Initiation of warfarin therapy should be tailored to the patient's clinical situation, while assessment to identify possible risks and benefits of treatment should be carried out by the physician and clinical pharmacist to identify any contraindications. Prior to treatment initiation, patients should be given detailed information about warfarin treatment and made aware of possible treatment alternatives. Following the decision to start warfarin the patient's target INR range, treatment duration and initial warfarin dose should be selected. The patient is referred to the pharmacist-led 'Anticoagulation Review Clinic' and for regular INR monitoring.

During the initial MUR session, the community pharmacist is to document the medical and medication history in the 'Anticoagulation and Medication Profile' (Appendix 2) and perform medication reconciliation to identify DRPs. The patient is provided with anticoagulation education and the pharmacist must ensure that the patient understands treatment and the importance of ongoing INR monitoring and regular MUR sessions. Follow-up MUR sessions are performed every six months for continuous educational interventions and medication reconciliation to identify DRPs.

The present study reported improvement in patient anticoagulation knowledge, adherence and INR control following pharmacist intervention during the MUR session,

hence implementation of an 'Anticoagulation Review Clinic' may potentially increase the number of patients who would be eligible for POC INR testing in community pharmacies.

The findings of the study were disseminated as a:

- Poster presentation titled 'Safer Anticoagulation Management in the Community: A Pharmacist-Led Approach' at the Maltese Cardiac Society Conference, October 2016
- Poster presentation titled 'Pharmacist-led medicine use review for patients on warfarin' at the 77th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences, in Seoul, Republic of Korea, September 2017.
- Poster discussion presentation titled 'Pharmacist-led Medicine Use Review for Patients on Anticoagulation Therapy' at the 46th European Society of Clinical Pharmacy (ESCP) Annual Symposium, in Heidelberg, Germany, October 2017 (Appendix 8).

4.2 Study limitations

A pre-post single-arm research methodology was used and no control group was investigated which may have compromised the internal validity of the study. Patients were recruited by convenience sampling as contact with participants could only be performed during pharmacy hours when patients collected their medications through the POYC scheme. The semi-structured interview technique selected for interaction between the pharmacist researcher and patient may have contributed to incomplete or

unclear data due to self-reporting bias. The absence of official standardised patient health records may have resulted in inappropriate documentation of medical and drug history since the researcher relied on the accuracy of the self-reported information provided by patients.

Various efforts have been made by the pharmacist researcher to ensure clinical judgment and consistency when classifying the identified DRPs however it was difficult to eliminate the risk of different interpretations of the identified problems. The clinical significance of the identified DRPs and recommendations were not assessed by another health professional apart from the pharmacist researcher. Due to restrictions in Maltese legislation, where pharmacist prescribing is not yet permitted, a true assessment of the outcomes of POCT INR monitoring and dose adjustments by the pharmacist researcher could not be assessed.

The use of written reactive notifications to communicate the pharmacist researcher's recommendations with the physician instead of multidisciplinary discussion may have resulted in a lower rate of implemented recommendations.

INR control was assessed over a short period of two months pre- and post-intervention. INR results were retrospectively audited and confounding variables such as warfarin duration, changes in medication and adherence were not taken into consideration. The Rosendaal linear interpolation method makes assumptions that may result in over- or underestimation of INR control.

Due to time limitations patients were only followed-up once after the MUR session hence it was not possible to assess the long-term impact of pharmacist recommendations and if implementation of the recommendations led to improved clinical outcomes.

4.3 Recommendations for further study

Further study should be carried out over a longer period to assess the impact of follow-up MUR sessions. A multi-centre study with the participation of a larger number of community pharmacists to investigate the impact of pharmacist-led MUR and evaluate patient treatment outcomes and long-term benefits of both intervention and control groups (no intervention), may result in better inferences.

In Malta, provision of MUR in community pharmacies is considered as an innovative service. A national assessment on the roll out and expansion of a pharmacist-led MUR service is recommended to be performed on different patient populations to further investigate the feasibility of MUR service provision and identify the advantages and disadvantages of the framework proposed in the study. The findings of the study should be used as a basis to design the service, develop high quality official and standard guidelines and formulate necessary accreditation and training modules for pharmacists, to ensure provision of a standardised optimal service that safeguards patient health.

Various studies confirm a lack of motivation for pharmacists to start offering MUR and expand their professional responsibility (van Mil et al, 2001; Buhagiar, 2007; Bryant et al, 2009; Azzopardi, 2010; Rieck and Pettigre, 2013; Sanchez and de las

Mercedes, 2013; Mehralian et al, 2014). Pharmacist perception was not assessed in the present study. Further studies should be carried out to evaluate community pharmacist perception and acceptance of the role of the community pharmacists in medication management, provision of pharmaceutical care through MURs and anticoagulation management services which include adjustment of warfarin doses. Further investigation to determine physician perception on expansion of the clinical role of the community pharmacists is also recommended.

Robust pharmacoecomonic studies on MUR services are limited (Blenkinsopp et al, 2012). It is recommended that a pharmacoeconomic study is performed to analyse the cost-effectiveness of community pharmacist-led MURs by assessing the effect of on national medication expenditure, consumption and medication wastage.

Introduction of POCT pharmacogenetic testing with the aim to achieve individualised genotype-guided warfarin dosing may lead to improved dosing, however studies on the benefits of pharmacogenetic testing are still ongoing. A similar study to Marcatto et al (2016) in Brazil may be carried out in Malta to evaluate the effect of a population specific pharmacogenetic-based warfarin dosing algorithm on TTR.

4.4 Conclusions

The deficiency in patient knowledge on warfarin, non-adherence to warfarin and high incidence of DRPs prior to pharmacist intervention point to the need for comprehensive patient assessment that ensures patient-centered care to improve warfarin management in community practice. The proposed pharmacist-led MUR service framework is a specialised service that enables individualised treatment review and development of a

pharmaceutical care plan to check and balance DRPs, in collaboration with physicians, to optimise treatment management not limited to anticoagulation therapy.

Pharmacist intervention during the MUR resulted in a significant improvement in anticoagulation knowledge, adherence to warfarin, compliance to INR monitoring, INR control, quality of life, patient perception of the community pharmacist's roles and competences, and a reduction in the number of chronic medications. The high proportion of accepted clinical interventions recommended by the pharmacist researcher during the MUR suggests that a pharmacist-led MUR has the potential to improve therapeutic outcomes and patient safety. Patient willingness to attend a pharmacist-led MUR, if implemented, and patient satisfaction with the pharmacist's input during the MUR session, indicates that patients benefitted from the service and have confidence in the expansion of the clinical role of community pharmacists.

Evidence from this study could inform future national health service policies for anticoagulation and chronic disease management, to support the introduction of a community pharmacist-led MUR service in Malta to meet patient needs.

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Appendix 1

Pre- and post-intervention questionnaire in English and Maltese

Pre-intervention Questionnaire **Patient Number:_____**

Age	□ 18-29 □30-49 □50-69 □ >70
Gender	Male/Female
Level of Education	□ Primary □Secondary □Post-Secondary □Tertiary
Year Warfarin was started	□ <6 months □ 6 months – 1year □ 1 -5 years □ > 5 years

Section 1: Warfarin Knowledge Test

(The following are multiple choice questions choose the correct answer)

1. How do you rate your knowledge on warfarin?
□ Very Poor
□ Poor
□ Fair
□ Good
□ Very Good

2. Warfarin may be used to treat people:
a. that already have a thrombus (blood clot) or to prevent a thrombus (blood clot) from forming in patients at risk
b. that have high blood sugar levels
c. with high blood pressure
d. with severe wounds

3The INR test is a blood test:
a. that is rarely done while on warfarin
b. used to monitor your warfarin therapy
c. that checks amount of vitamin K in your diet
d. that can determine if you need to be on warfarin

4. A patient with an INR value above his/her target INR range:
a. is at an increased risk of developing a thrombus (clot)
b. is more likely to have drowsiness and fatigue from warfarin
c. is at an increased risk of bleeding
d. is less likely to experience side-effects from warfarin

5. A patient with an INR value below his/her target INR range:
a. is at an increased risk of bleeding
b. is at an increased risk of forming a thrombus (clot)
c. is more likely to have a skin rash from warfarin
d. is more likely to experience side-effects from warfarin

6. While on warfarin in which case should you attend the emergency department?
a. Formation of small bruises with minimal trauma
b. Dramatic increase in appetite
c. Nose bleeds which cannot be controlled by pressure
d. Gums which bleed for few seconds after teeth brushing

7. Which health professional should be informed that you are taking warfarin? (more than one option may be selected)
a. a pharmacist suggesting an over the counter medication, vitamins or a herbal supplement
b. a physician who is prescribing a medication
c. a dentist who will be performing a tooth extraction
d. a physician who is stopping a medication

8. You can distinguish between different strengths of warfarin tablets by what?
a. colour
b. shape
c. size
d. marking on the tablet

9. Which of the following interferes with how warfarin works? (more than one option may be selected)
a. medication
b. food and alcohol
c. vitamins and herbal supplements
d. exercise

10. Which of the following foods interfere with how warfarin works? (more than one option may be selected)
a. broccoli
b. carrots
c. cranberry juice
d. oranges

11. When is the best time to take warfarin?
a. at lunchtime
b. in the morning before breakfast
c. at the same time each day, ideally in the evening at around 5pm
d. when I remember (Any time of day)

12. The best thing to do if you forget to take a dose of warfarin? (More than one option may be selected)
a. double up the next day
b. Skip the dose
c. take the dose as soon as you remember if it's the same day
d. always inform the health care provider at the anticoagulation clinic when you go for the INR test

13. When is it safe to take a medication that interacts with warfarin?
a. if you take warfarin in the morning and the interacting medication at night
b. if your physician is aware of the interacting medication and increases INR monitoring
c. if you take warfarin every other day
d. it is never safe to take a medication that interacts with warfarin

Section 2: Warfarin Compliance Assessment Tool

1. What dose of warfarin are you currently taking?_____

2. Who prepares your medication? (More than one option may be selected)
a. I prepare my medication
b. The medication is prepared by a relative
c. The medication is prepared by a health care professional or a carer

3.i. Over the past two weeks were there any days when you missed your warfarin dose?
a. Yes
b. No

3.ii. If yes?
a. Missed 1 Dose
b. Missed 2 Doses
c. Missed 3 or more doses
d. Do not know

4. Over the past two weeks were there any days when you took additional doses of warfarin?
a. Yes
b. No

4.ii. If yes?
a. Took 1 extra dose
b. Took 2 extra doses
c. Took 3 or more extra doses
d. Do not know

5. Do you find it difficult to modify the warfarin dose as instructed from the anticoagulation clinic?
a. Yes
b. No

6. Were there times when you did not change the dose as recommended?
a. Yes
b. No

6.ii. If yes, for what reason? _____

7.i. Did you ever miss going for an INR test?
a. Yes
b. No

7ii. If yes, for what reason? _____

8. Does your consumption of leafy green vegetables vary from week to week?
a. Yes, it varies
b. No, I eat consistent amounts
c. I do not consume any leafy green vegetables
d. Not sure

9. Does your alcohol consumption change throughout the week?
a.Yes, I don't take any alcohol
b.Yes I take _____
c. No
d. Not sure

Pre- intervention Questionnaire Section 3: Perceptions on the current anticoagulation service

1.Where do you usually have your INR checked?
a. Anticoagulation Clinic Mater Dei Hospital
b. Health Centre
c. Family Doctor
d. At home

2.How is your blood drawn during your INR test?
a. From the arm by venepuncture
b. From the finger tip

3. How are the results and dosing instructions communicated to you?
a. By telephone
b. By post
c. Immediately during the visit
d. Other_____

4. How do you prefer to receive the INR results and new dosing instructions?
a. By telephone
b. By post
c. Immediately during the visit
d. Email or SMS
e. Other_____

5.i. Was counselling on anticoagulation provided when you were prescribed warfarin ?
a.Yes
b. No

5.ii. If yes by who?
a.Pharmacist
b.Physician
c.Nurse
d.Other _____

Rate the following where 1= you are not satisfied at all with the service
5= you are very satisfied with the service

		1	2	3	4	5
6	How satisfied are you with the current anticoagulation service					
7	How satisfied are you with the advice and information you are currently receiving					

8.i. Do you feel that a change or an improvement of the current anticoagulation system is required?
a. Yes
b. No
c. Not sure

8ii. If Yes, what do you think needs to be changed or improved?

_____

Post-intervention Questionnaire Section 3: Perception on the pharmacist-led service

1. Did the pharmacist provide you with new information?
a. Yes
b. No
c. Not sure

2.Rate your level of agreement with the statements below regarding the pharmacist's intervention?

Please rank the below from 1 to 5. (Strongly disagree to Strongly agree)

		1. Strongly Disagree	2. Disagree	3. Neither agree nor disagree	4. Agree	5. Strongly Agree
a	The pharmacist has spent enough time with me to discuss my treatment needs					
b	Since I have attended the pharmacist-led clinic, I feel that I am more knowledgeable about my anticoagulation treatment					
c	The printed material provided has been beneficial					
d	If the proposed system is implemented, I will be willing to start making use of the system					

3. Has the pharmacist's contribution in the management of warfarin changed your view on how the pharmacist can be of help in patient care?
a. Yes
b. No
c. Not sure

4. In what aspects do you feel that the service helped you?

_____

_____

5. Was there anything that bothered you or should be improved during the service?

_____

_____

6. Do you have any additional suggestions?

_____

_____

Section 4: Assessment of the contribution of the pharmacist intervention

1. How much do you agree with the statements below?
   Please rank the below from 1 to 5. (Strongly disagree to Strongly agree)

		1. Strongly Disagree	**2. Disagree**	**3. Neither agree nor disagree**	**4. Agree**	**5. Strongly Agree**
1.	I feel that the need for frequent warfarin dose adjustments complicate my treatment					
2.	I feel that warfarin affects my quality of life					
3.	I feel confident that the pharmacist can manage my warfarin treatment safely					
4.	I feel that the pharmacist intervention will improve my overall health and contribute to better INR control					
5.	I think that the pharmacist is able to provide me with education that will improve my confidence in handling warfarin					
6.	I will find it useful to be able to discuss my warfarin treatment with the pharmacist when I attend for the testing					
7.	I will feel comfortable if my pharmacist had to perform any warfarin dose changes					
8.	I will feel comfortable if the pharmacist reviews my medication and provides any necessary recommendations					

Kwestonarju qabel l-intervent tal-ispizjar **Numru tal-pazjent:_____**

Età	□ 18-29 □30-49 □50-69 □ >70
Ġeneru	Raġel/Mara
Livell ta' Edukazzjoni	□ Primarja □Sekondarja □Post-Sekondarja □Terzjarja
Kemm ilek li bdejt il-warfarina	□ <6 xhur □ 6 xhur – sena □ 1 -5 snin □ > 5 snin

Taqsima 1: Eżami tal-għarfien fuq il-warfarina

Agħżel it-tweġiba t-tajba

1. Irrata l-livell tal-għarfien tiegħek fuq il-warfarina;
☐ ħażin ħafna
☐ ħazin
☐ mhux ħażin
☐ tajjeb
☐ tajjeb ħafna

2. Il-warfarina tista' tintuża għall-persuni:
☐ a. li għandhom embolu (*clot*) jew biex tippreveni embolu (*clot*) milli jifforma f'pazjenti li għandhom ir-riskju
☐ b. li għandhom iz-zokkor għoli
☐ c. li għandhom il-pressjoni għolja
☐ d. li għandhom feriti gravi

3. L-INR test huwa test tad-demm:
☐ a li rari jintuża għal nies li jieħdu l-warfarina
☐ b. li jiddetermina d-doża tal-warfarina li għandek tieħu
☐ c. li jiċċekkja l-ammont ta' Vitamina K li tittieħed fid-dieta
☐ d. li jiddetermina jekk għandekx bżonn tibda l-warfarina

4. Pazjent b'INR għoli ħafna:
☐ a. għandu riskju ikbar li jifformalu embolu (*clot*)
☐ b. għandu riskju ikbar li jsofri bi sturdament u għeja minħabba l-warfarina
☐ c. għandu riskju ikbar li jitlef id-demm
☐ d. għandu ċans iżgħar li jkollu iktar *side-effects*

5. Pazjent b'INR baxx ħafna:
☐ a. għandu riskju ikbar li jitlef id-demm
☐ b. għandu riskju ikbar li jtifformalu embolu (*clot*)
☐ c. għandu ċans ikbar li jiżviluppa raxx minħabba l-warfarina
☐ d. għandu ċans ikbar li jkollu iktar *side-effects*

6. Meta tkun qed tieħu l-warfarina f'liema każi għandek tmur l-emergenza?
☐ a. meta tinnota xi tbenġil żgħir
☐ b. meta l-aptit jiżdiedlek ħafna aktar min-normal
☐ c. meta tinfaraġ u ma tkunx tista' żżomm id-demm minkejja li tagħfas imnieħrek
☐ d. meta joħroġ ftit demm mill-ħanek meta taħsel snienek

7. Lil min minn dawn għandek dejjem tinforma li tieħu l-warfarina? (Tista' tagħżel iktar minn risposta waħda)
☐ a. spiżjara li qiegħda tissuġġerixxi xi mediċini mingħajr il-ħtieġa ta' riċetta, vitamini jew supplimenti magħmula mill-ħxejjex
☐ b. tabib li se jordnalek xi mediċina
☐ c. dentist li se jaqlagħlek xi sinna
☐ d. tabib li se jwaqqaflek xi mediċina

8. Kif tista' tiddistingwi bejn id-dożi differenti tal-warfarina?
☐ a. kulur
☐ b. forma
☐ c. qies
☐ d. marki fuq il-pilloli

9. Liema minn dawn jinterferixxu ma' kif taħdem fil-ġisem il-warfarina? (Tista' tagħżel iktar minn risposta waħda)
☐ a. mediċina oħra
☐ b. ikel u alkoħol
☐ c. vitamini u supplementi magħmula mil-ħxejjex
☐ d. eżerċizzju

10. Liema minn dan l-ikel jinterferixxi ma'kif taħdem fil-ġisem il-warfarina? (Tista'tagħżel iktar minn risposta waħda)
☐ a. brokkoli
☐ b. karrotti
☐ c. *cranberry juice*
☐ d. laringġ

11. Liema hu l-aħjar ħin biex tieħu l-warfarina?
☐ a. mal-ikla ta' nofsinnhar
☐ b. filgħodu qabel il-kolazzjon
☐ c. fl-istess ħin tal- ġurnata, idealment għal xil-ħamsa ta' filgħaxija
☐ d. xħin niftakar (kwalunkwe ħin tal-ġurnata)

12. X'inhi l-aħjar ħaġa li għandek tagħmel jekk tinsa tieħu l-warfarina fil-ħin? (Tista'tagħżel iktar minn risposta waħda)

☐ a. tieħu doża doppja d-darba li jmiss

☐ b. taqbeż id-doża

☐ c. tieħu d-doża xħin tiftakar jekk tkun għadha l-istess ġurnata

☐ d. tinforma dejjem lit-tabib jew in-nurse tal- *anticoagulation clinic* meta tmur għat-test tal-INR test

13.Meta huwa sikur li tieħu xi mediċini li jinteraġixxu mal-warfarina:

☐ a. jekk tieħu l-warfarina filgħodu u l-mediċina li tinteraġixxi billejl

☐ b. jekk t-tabib ikun konxju li l-mediċina tinteraġixxi u jżied il-frekwenza tat-testijiet tal-INR

☐ c. jekk tieħu l-warfarina darba iva u darba le

☐ d. qatt ma huwa sikur li tieħu mediċina li tinteraġixxi mal-warfarina

Taqsima 2:

1. X'doża ta' warfarina qed tieħu bħalissa?

_____

2. Min jippreparalek il-mediċini tiegħek? (Tista'tagħżel iktar minn risposta waħda)

☐ a. Jiena nipprepara l-mediċini tiegħi

☐ b. Il-mediċini jippreparawhomli xi famljari tiegħi

☐ c. Il-mediċini jippreparahomli xi profesjonist tas-saħħa jew *carer*

3i. Fl-aħħar ġimagħtejn kien hemm ġranet meta nsejt tieħu l-warfarina?

☐ a. Iva

☐ b. Le

3ii. Jekk Iva? ☐ a. Qbiżt doża waħda
☐ b. Qbiżt żewġdoži
☐ c. Qbiżt tliet dożi jew iktar
☐ d. Ma nafx

4. Fl-aħħar ġimagħtejn kien hemm ġranet fejn ħadt iktar dożi milli suppost?

☐ a. Iva

☐ b. Le

Jekk Iva? ☐ a. Ħadt doża żejda
☐ b. Ħadt żewġ dożi żejda
☐ c. Ħadt tliet dożi żejda
☐ d. Ma nafx

5. Issibha diffiċli biex tbiddel id-doża tal-warfarina skont l-struzzjonijiet tal-*anticoagulation clinic*?

☐ a. Iva
☐ b. Le

6i. Kien hemm drabi meta d-doża ma biddilthiex kif irrakkomandawlek?

☐ a. Iva
☐ b. Le

6ii) Jekk iva, għal liema raġuni?

_____

7i. Kien hemm drabi meta ma mortx għat-test tal-INR?

☐ a. Iva
☐ b. Le

7ii. Jekk iva, għal-liema raġuni? _____

8. L-ammont ta' ħaxix aħdar li tiekol matul il-ġimgħa jvarja minn ġimgħa għal oħra?

☐ a. Iva, invajra
☐ b. Le, niekol l-istess ammonti
☐ c. Ma nikolx ħaxix aħdar
☐ d. Mhux ċert

9. Matul il-ġimgħa tikkonsma l-istess ammont ta' alkoħol?

☐ a. Iva, ma nixrob xejn
☐ b. Iva, nieħu _____
☐ c. Le
☐ d. Mhux ċert

Kwestonarju qabel l-intervent tal-ispizjar: Taqsima 3: Mistoqsijiet fuqis-servizz li qed jiġi mogħti bħalissa

1. Normalment fejn tmur tiċċekkjal-INR?

☐ a. *Anticoagulation Clinic* l-isptar Mater Dei
☐ b. *Health Centre*
☐ c. Għand it-tabib tal-familja
☐ d. Id-dar

2. Minn fejn jeħdulek id-demm waqt t-test tal-INR?

☐ a. Mill-vina
☐ b. Minn subgħajk

3. Kif jiġu kkomunikati r-riżultati tal-INR u d-dożi l-ġodda tal-warfarina?

☐ a. Bit-telefown
☐ b. Bil-posta
☐ c. Waqt il-vista
☐ d. Oħrajn _____

4. Kif tippreferi li jiġukkomuni kati r-riżultati tad-demm u d-dożi l-ġodda tal-warfarina?

☐ a. Bit-telefown
☐ b. Bil-posta
☐ c. Waqt il-vista
☐ d. Email jew SMS
☐ e. Oħrajn_____

5i. Irċevejt tagħrif fuq il-warfarina fil-bidu li bdejt teħodha?

☐ a. Iva
☐ b. Le

5ii. Jekk iva, mingħand min?

☐ a. Spiżjara
☐ b. Tabib
☐ c. Nurse
☐ d. Oħrajn _____

Agħti marka lil dawn l-istqarrijiet (1= m'inti sodisfatt xejn bis-servizz; 5= sodisfatt ħafna bis-servizz)

		1	2	3	4	5
6.	Kemm inti sodisfatt bis-servizz li qed tiġi tingħata bħalissa					
7.	Kemm inti sodisfatt bil-pariri u l-informazzjoni li qed tirċievi bħalissa					

8.i. Taħseb li hemm bżonn tibdil jew titjib fis-sistema użata bħalissa mill-*anticoagulation clinic*?

☐ a. Iva
☐ b. Le
☐ c. Mhux ċert

8.ii. Jekk iva, x'taħseb li hemm bżonn jinbidel jew jitranġa?

_____

Kwestjonarju wara l-intervent tal-ispizjar: Taqsima 3: Mistoqsijiet fuq is-servizz propost

1. L-ispiżjara provditlek informazzjoni ġdida?
☐ a. Iva
☐ b. Le
☐ c. Mhux ċert

2. Kemm taqbel mal-istqarrijiet t'hawn taħt fuq l-intervent tal-ispizjar? Agħti marka bejn 1 (Ma naqbel xejn) sa 5 (Naqbel ħafna)

		1. Ma naqbel xejn	**2. Ma naqbilx**	**3. Newtrali**	**4. Naqbel**	**5. Naqbel ħafna**
a	Il-ħin użat mill-ispiżjara għall-intervent kien biżżejjed biex niddiskutu l-bżonnijiet mediċi tiegħi					
b	Minn meta attendejt għall-*anticoagualtion clinic* immexxi mill-ispiżjara nħossni li qed nifhem it-trattament tiegħi aħjar					
c	Il-materjal edukattiv li tawni kien ta' benefiċċju					
d	Jekk is-sistema li qed tiġi proposta tkun implementata nibda nagħmel użu minnha					

3. Il-kontribuzzjoni tal-ispiżjara fl-immaniġġjar tal-warfarina biddlitlek l-idea ta' kif l-ispiżjara tista'tkun ta' benefiċċju għas-saħħa ħolistika tal-pazjent?
☐ a. Iva
☐ b. Le
☐ c. Mhux ċert

4. F'liema aspetti taħseb li għenek is-servizz offrut?

_____

_____

5. Kien hemm xi affarijiet li dejquk jew li taħseb li jistgħu jittjiebu waqt is-servizz offrut?

_____

6. Għandek xi suġġerimenti oħra?

_____

Taqsima 4: Mistoqsijiet fuq l-intervent tal-ispiżjara

1. Kemm taqbel mal-istqarrijiet t'hawn taħt? Agħti marka bejn 1 (Ma naqbel xejn) sa 5 (Naqbel ħafna)

		1. Ma naqbel xejn	**2. Ma naqbilx**	**3. Newtrali**	**4. Naqbel**	**5. Naqbel ħafna**
1	Inħoss li l-bdil frekwenti fid-dożi tal-warfarina jikkomplikaw il-mediċina tiegħi					
2	Inħoss li l-warfarina taffettwa l-kwalità tal-ħajja tiegħi					
3	Inħossni kunfidenti li l-ispiżjara tista' timmaniġġja t-trattament li nieħu tal-warfarina b'mod sikur					
4	Inħoss li l-intervent tal-ispiżjara jista' jtejjeb is-saħħa globali tiegħi u jikkontribwixxi għall-kontroll aħjar tal-INR					
5	Naħseb li l-ispiżjara tista' tgħinni ntejjeb l-għarfien dwar il-warfarina li nżid il-kunfidenza li biha nimmaniġġja l-warfarina					
6	Insibha utli li nkun nista' niddiskuti t-trattament tal-warfarina mal-ispiżjara meta nattendi għall-ittestjar					
7	Inħossni komdu kieku li l-ispiżjara kellha tbiddilli d-doża tal-warfarina					
8	Inħossni komda kieku l-ispiżjara tirrevedi l-mediċini li nieħu u tagħtini r-rakkomandazzjonijiet tagħha					

Appendix 2

‘Anticoagulation and Medication Profile’ in English and Maltese

Anticoagulation

and

Medication Profile

Name: _____

ID Card: _____

Patient's Name

Personal Details		
Name and Surname		
Id card number		
Address		
Contact Number		
Date of Birth		
Gender		
Drug Allergies		
Previous Drug Adverse Reactions		
Past / Current Medical Conditions		
□ Hypertension	□ Asthma/COPD	□ Chronic Mood Disease
□ Atrial Fibrillation	□ GORD/Gastric Ulcers	□ Schizophrenia
□ Heart Failure	□ Liver Disease	□ Rheumatoid Arthritis
□ Hypercholesterolemia	□ Renal Disease	□ Osteoporosis
□ Heart Valve Replacement	□ Hypothyroidism	□ Fibromyalgia
□ Ischaemic Heart Disease	□ Hyperthyroidism	□ Glaucoma
□ Diabetic	□	□
□	□	□
Lifestyle factors		
Smoking Status	Never / Past / Current - Number of cigarettes	
Alcohol Consumption	Never / Number of units consumed	

Patient's Name

Medication Profile									
Active Ingredient	Brand Name	Dose	Formulation	Dosage Regimen				Indication for use	Counselling Points and Administration Instructions
				Breakfast	Lunch	Dinner	Bed time		

Date : _____

Patient's Name

Pharmaceutical Care Plan

Action Plan			
Issue	**Recommendation**	**For consideration by**	**Outcome**
		□ **Patient** □ **Pharmacist** □ **Physician** □ **Other:**	
		□ **Patient** □ **Pharmacist** □ **Physician** □ **Other:**	
		□ **Patient** □ **Pharmacist** □ **Physician** □ **Other:**	
		□ **Patient** □ **Pharmacist** □ **Physician** □ **Other:**	
		□ **Patient** □ **Pharmacist** □ **Physician** □ **Other:**	
		□ **Patient** □ **Pharmacist** □ **Physician** □ **Other:**	

Patient's Name

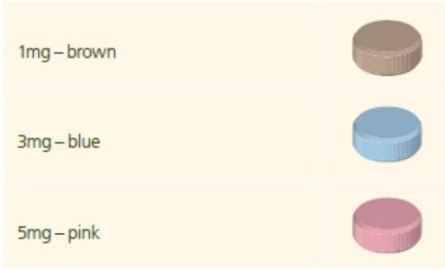
Warfarin Patient Information

Warfarin slows down the blood clotting process and is used to prevent excessive blood coagulation, avoiding formation of thrombi in the veins and arteries.

The INR test measures the time blood takes to clot. It is used to monitor warfarin effects on the blood clotting time. Regular monitoring of the INR level is important to optimise the warfarin dose so that the blood clotting time is maintained within the tar-get range.

- A high INR value needs a reduction in the warfarin dose.
- A low INR value needs an increase in the warfarin dose.

- Warfarin can be found in three different doses.
- You may need different tablets to make up your dose. Always confirm with your pharmacist that you are administering the right dose



Points to keep in mind:

- Always take the warfarin dose at the **same time** of the day - ideally around 5pm. Do not take double the dose.

- If you **miss a dose**, and you realise on the same day, take it at a later time. If you realise that you have missed your dose by a day, do not take any extra dose. When this happens, duly note the date and inform the healthcare professional during your next appointment. Use pill boxes or calendars so that they help you remember to take the dose.

- The most serious side effect of warfarin is **bleeding**. Contact your doctor immediately if you experience serious bleeding such as prolonged nose bleeds, blood in urine and faeces, coughing up of blood and severe headaches.

- Various prescription medicine, over the counter, vitamins and herbal products may interact with the warfarin therefore it is important to **inform health professionals** (doctors, dentists, pharmacists, nurses) that you are taking warfarin.

    - Drugs containing non-steroidal anti-inflammatory drugs such as diclofenac and ibuprofen should be avoided and only painkillers which are **paracetamol** or codeine-based are acceptable.

    - If you require starting or stopping a medication, frequent INR tests may be required to ensure that the INR remains within the desired range.

- Food containing high levels of **Vitamin K** like broccoli and spinach may alter warfarin action. It is important to maintain a consistent intake of these vegetables. Cranberry juice must be avoided altogether.

- Moderate the **alcohol** consumption, limit to 1 or 2 drinks per day.

- When on warfarin one can perform all normal daily activities. It is however important to avoid activities that place you at **risk of injury** associated with bleeding.

- Some illness may change the effect of warfarin. Contact your doctor when you experience vomiting, fever, diarrhoea or infection.

It is important that

- INR testing appointments are never missed.

- The warfarin dose is changed as required based on the INR test result. Take warfarin dose exactly as indicated, always confirm with your pharmacist that you are taking the right dose.

Patient's Name

Warfarin Dosing Calendar

Month of					Year:	
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**

Profil Mediku

u tal-Anticoagulation

Isem: _____

Numru tal-ID card: _____

Isem il-pazjent

Dettalji Personali		
Isem u Kunjom		
Numru tal-ID		
Indirizz		
Numru ta-telefown		
Data tat-twelid		
Ġeneru		
Allerġiji magħrufa marbuta mal-mediċini		
***Side effects* assoċjati mal-mediċini**		
Kundizzjonijiet tas-saħħa fl-imgħoddi u fil-preżent		
□ Hypertension (Pressjoni għolja)	□ Asthma/COPD	□ Chronic Mood Disease
□ Atrial Fibrillation	□ GORD/Gastric Ulcers	□ Schizophrenia
□ Heart Failure	□ Liver Disease (Mard tal-fwied)	□ Rheumatoid Arthritis
□ Hypercholesterolemia	□ Renal Disease (Mard tal-kliewi)	□ Osteoporosis
□ Heart Valve Replacement	□ Hypothyroidism	□ Fibromyalgia
□ Ischaemic Heart Disease	□ Hyperthyroidism	□ Glaucoma
□ Diabetic (Dijabete)	□	□
□	□	□
Tipjip	Qatt /Passat /Bħalissa- Numru ta' sigaretti	
Konsum tal-alkoħol	Qatt /Numru ta'units	

Isem il-pazjent

Profil tal- Mediċini									
Ingredjent Mediċinali Attiv	**Isem tad-ditta**	**Doża**	**Għamla farmaċewtika**	**Meta għandek tieħu l-Mediċini**				**Għal xiex ġiet indikata biex tintuża**	**Istruzzjonijiet għal kif tieħu l-mediċina**
				Filgħodu	**F'nofsinhar**	**Filgħaxija**	**Qabel l-irqad**		

Data : _____

<u>*Isem il-pazjent*</u>

Pjan ta' Kura Farmaċewtika

Pjan t'Azzjoni			
Problema	**Rakkomandazzjoni**	**Biex tiġi kkunsidrata minn**	**Riżultat**
		☐ Pazjent ☐ Spiżjar ☐ Tabib ☐ Oħrajn:	
		☐ Pazjent ☐ Spiżjar ☐ Tabib ☐ Oħrajn:	
		☐ Pazjent ☐ Spiżjar ☐ Tabib ☐ Oħrajn:	
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		☐ Pazjent ☐ Spiżjar ☐ Tabib ☐ Oħrajn:	
		☐ Pazjent ☐ Spiżjar ☐ Tabib ☐ Oħrajn:	

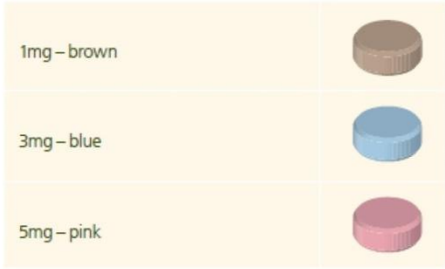
Informazzjoni tal-pazjent li jieħu l-warfarina

Il-warfarina tnaqqas il-proċess ta' tagħqid tad-demm u huwa użat biex jipprevjeni koagulazzjoni tad-demm eċċessiv, filwaqt li tevita formazzjoni ta' trombi fil-vini u arterji.

It-test tal-INR ikejjel il-ħin li d-demm jieħu biex jagħqad. Jintuża biex jimmoniterja l-effetti tal-warfarina fuq il-ħin tat-tagħqid tad-demm. Moniteraġġ regolari tal-livelli tal-INR huwa importanti biex jimmeljoraw id-doża tal-warfarina sabiex il-ħin tat-tagħqid tad-demm jinżamm fi ħdan il-firxa tal-mira.

- Valur għoli ta' INR ikollu bżonn tnaqqis fid-doża tal-warfarina.
- Valur baxx ta' INR ikollu bżonn żieda fid-doża tal-warfarina.

- Il-warfarina tista' tinstab fi tliet dożi differenti.
- Hemm mnejn ikollok bżonn pilloli differenti li jagħmlu d-doża għalik. Dejjem ikkonferma li qed tieħu d-doża t-tajba mal-ispiżjar tiegħek.



Punti xi żżomm f'moħħok:

- Dejjem ħu d-doża tal-warfarina fl-istess ħin tal-ġurnata – idealment għall-ħabta tal-5pm. Tiħux id-doppju tad-doża.

- Jekk tinsa tieħu d-doża u tinduna dakinhar stess, ħudha iktar tard. Jekk tinduna li ma ħadtx id-doża l-għada, tiħux id-doża doppja. Meta jiġri hekk, ħu nota tad-data u informa lit-tabib tiegħek fl-appuntament li jkun imissek. Uża l-kaxxi tal-pilloli jew il-kalendarji sabiex jgħinuk tiftakar tieħu d-doża.

- L-iktar side effect serju tal-warfarina huwa l-fsada. Ikkuntattja lit-tabib tiegħek minnufih jekk tesperjenza fsada serja bħal fġir fit-tul, demm fl-awrina jew fl-ippurgar, sogħla tad-demm jew uġigħ ta' ras kbira.

- Diversi mediċini li jkunu preskritti mit-tabib, oħrajn li m'hemmx bżonn riċetta tat-tabib għalihom, vitamini u prodotti veġetali jistgħu jinteraġixxu mal-warfarina u għalhekk huwa importanti li tinforma lill-professjonisti tas-saħħa (tobba, dentisti, spiżjara, infermiera) li tkun qed tieħu l-warfarina.
    - Evita li tieħu mediċini kontra l-infjammazzjoni li ma fihomx steroids bħad-diclofenac u l-ibuprofen u għall-uġigħ ħu mediċini li fihom il-paracetamol jew il-codeine.

    - Jekk ikollok bżonn tibda jew twaqqaf xi medikazzjoni, jaf ikollok bżonn testijiet tal-INR frekwenti sabiex tassigura li l-INR jibqa' fil-firxa mixtieqa.

- Xi ikel li fih livelli għoljin ta' Vitamina K, bħall-brokkoli u l-ispinaċi, jaf jibdel l-azzjoni tal-warfarina. Huwa importanti li jinżamm ammont konsistenti ta' teħid ta' dawn il-ħxejjex. Il-ġus tal-cranberries għandu jiġi evitat.

- Għandek timmodera l-konsum tal-alkoħol għal-limitu ta' 1 jew 2 drinks fil-ġurnata.

- Meta tkun qed tieħu l-warfarina, tista' tibqa' tagħmel l-attivitajiet normali ta' kuljum. Madankollu huwa importanti li tevita attivitajiet li jafu jpoġġuk f'riskju ta' korriment assoċjat mal-fsada.

- Xi mard jista' jbiddel l-effetti tal-warfarina. Ikkuntattja t-tabib jekk tesperjenza xi remettar, deni, dijarea jew infezzjoni.

Huwa importanti li:

- Qatt ma titlef appuntamenti ta' testijiet tal-INR.
- Id-doża tal-warfarina tinbidel kif meħtieġ skont ir-riżultat tat-test tal-INR. Għandek tieħu d-doża tal-warfarina eżattament kif indikat u kkonferma d-doża l-korretta mal-ispiżjar tiegħek.

Isem il-pazjent

Kalendarju – Kif għandek tieħu l-warfarina

Ix-Xahar					Sena:	
Il-Ħadd	**It-Tnejn**	**It-Tlieta**	**L-Erbgħa**	**Il-Ħamis**	**Il-Ġimgħa**	**Is-Sibt**
Il-Ħadd	**It-Tnejn**	**It-Tlieta**	**L-Erbgħa**	**Il-Ħamis**	**Il-Ġimgħa**	**Is-Sibt**
Il-Ħadd	**It-Tnejn**	**It-Tlieta**	**L-Erbgħa**	**Il-Ħamis**	**Il-Ġimgħa**	**Is-Sibt**
Il-Ħadd	**It-Tnejn**	**It-Tlieta**	**L-Erbgħa**	**Il-Ħamis**	**Il-Ġimgħa**	**Is-Sibt**
Il-Ħadd	**It-Tnejn**	**It-Tlieta**	**L-Erbgħa**	**Il-Ħamis**	**Il-Ġimgħa**	**Is-Sibt**

Appendix 3

Covering Letter in English and Maltese

Dear Sir/Madam,

I, Elena Marie Mifsud, am a pharmacist currently reading for a Doctorate in Pharmacy with the University of Malta in collaboration with the University of Illinois in Chicago, will be undertaking a research project entitled '**Safer Anticoagulation Management in the Community: A Pharmacist-led Approach'** under the supervision of Prof. Anthony Serracino-Inglott, Professor at the Department of Pharmacy and Dr. Francesca Wirth, Research Support Officer at the Department of Pharmacy, University of Malta.

You have been identified to participate in this research which involves the following:

Aim of research and how will you benefit?

The aim of this study is to develop and evaluate the impact of a new focused anticoagulation service, led by community pharmacists, with the overall goal being to improve the safety profile of warfarin management in community practice.

Your involvement

You will be invited to attend two clinical sessions. During the first session your medical and medication history will be compiled. The data collected will be used to develop an individualised pharmaceutical care plan to monitor and prevent anticoagulation therapy-related complications. An INR test may be performed by obtaining a drop of capillary blood from your fingertip and monitored by the coagulometer, *CoaguChek®XS*. A counselling session will then be provided. After 2 months a follow up session will be performed to assess the impact of the pharmacist intervention. During the clinical sessions you will be asked to fill a questionnaire which will be performed as a semi-structured interview.

Other important information

Participation in this research is entirely voluntary. The intervention and testing are free of charge and will be carried out in the pharmacy. There are no risks when participating in this study. This intervention will performed in addition to the test normally performed at the ACC or health centre. The information gathered will be kept strictly confidential and used solely for the purpose of the research according to the Data Protection Act. You may discontinue participation in this research at any time without any prejudice.

If you agree to participate, you are requested to complete your details below so that I will contact you to set an appointment. For more information, kindly contact me by phoning on 79413924 or by sending an email to emif0008@um.edu.mt.

Thanking you in anticipation for your contribution in this study.

Elena Marie Mifsud B.Sc. Pharm. Sci. (Hons.), M.Pharm.

Name: _____ Contact number: _____

Għażiż/a Sinjur/a,

Jiena, Elena Marie Mifsud, spiżjara li qed nagħmel id-Dottorat fil-Farmaċija mal-Università ta' Malta b'kollaborazjoni mal-Università ta' Illinois f'Chicago, se nkun qed nagħmel proġett ta' riċerka msejjaħ '**Safer Anticoagulation Management in the Community: A Pharmacist-led Approach**' taħt is-superviżjoni tal-Prof. Anthony Serracino Inglott, Professur fid-Dipartiment tal-Farmaċija tal-Università ta' Malta u Dr Francesca Wirth, *Research Support Officer* fl-istess Dipartiment.

Inti ġejt identifikat biex tipparteċipa f'dan l-istudju li jinkludi:

Skop tar-riċerka u kif se tibbenefika

L-iskop ta' dan l-proġett hu li jiġi stabbilit u eżaminat l-impatt ta' servizz ġdid għall-pazjenti li jieħdu l-warfarina mogħti mill-ispiżjara b'għan li jtejjeb l-effett u jnaqqas il-kumplikazzjonijiet tal-warfarina.

L-involviment tiegħek

Inti se tkun mistieden biex tattendi għal żewġ sessjonijiet. Waqt l-ewwel sessjoni l-ispiżjara tanalizza l-lista tal-mediċini u l-istorja medika tiegħek. L-informazjoni miġbura se tkun użata biex l-ispiżjara toħloq pjan farmaċewtiku għall-moneteraġġ u prevenzjoni ta' kumplikazzjonijiet relatati mal-użu tal-warfarina. Jista' jkun li jsirlek it-test tal-INR, dat-test isir billi tittieħidlek taqtira demm minn wieħed mis-swaba', u tiġi eżaminat bl-apparat *CoaguChek®XS*. Int se tingħata sessjoni edukattiva u wara xahrejn issir sessjoni oħra fejn jiġi evalwat l-impatt tal-intervent tal-ispiżjara. Waqt is-sessjonijiet int se tiġi mitlub twieġeb kwestjonarju f'forma ta' intervista biex tiġi evalwata s-sistema li qed tiġi proposta.

Iktar informazjoni importanti

Il-parteċipazzjoni tiegħek f'dan l-istudju hi totalment volontarja. Dawn is-sessjonijiet u t-test se jkunu offruti b'xejn u se jsiru fl-ispiżerija. M'hemm ebda riskju meta tipparteċpa f'dan l-istudju. Dan l-intervent se jsir komplementarju mat-test li normalment isir l-ACC jew fiċ-ċentru tas-saħħa u mhux minfloku. L-informazzjoni miġbura hija konfidenzjali u se tintuża għall-fini ta' dan l-istudju skont l-Att tal-Protezzjoni tad-Dara. Tista' tieqaf min dan l-istudju meta trid mingħajr ebda preġudizzi.

Jekk taqbel li tieħu sehem f'dan l-istudju inti mitlub/a li timla d-dettalji tiegħek hawn taħt biex inkun nista' nikkuntattjak biex isir appuntament. Għal aktar tagħrif u informazzjoni rigward dan l-istudju, tista' ċċempili fuq in-numru 79413924 jew tibgħatli *email* fuq emif0008@um.edu.mt. Nirringrazzjak bil-quddiem għas-sehem tiegħek f'dan l-istudju.

Elena Marie Mifsud B.Sc. Pharm. Sci. (Hons.), M.Pharm.

Isem: _____ Numru tat-telfon: _____

Appendix 4

Consent Form in English and Maltese

CONSENT FORM

I am a Maltese citizen and am over eighteen (18) year of age.

I have been asked to participate in a research study entitled:

Safer Anticoagulation Management in the Community: A Pharmacist-led Approach

The purpose and details of the study have been explained to me by **Elena Marie Mifsud**

and any difficulties which I raised have been adequately clarified.

I give my consent to the investigator to interview me and make the appropriate observations/tests or both or take necessary samples. I am aware of the inconveniences which this will cause.

I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from this study in which I am participating may be reported or published: however, I shall not be personally identified in any way, either individually or collectively, without my express written permission.

I am under no obligation to participate in this study and am doing it voluntarily.

I may withdraw from the study at any time, without giving any reason. This will not influence in any way the care and attention and treatment normally given to me.

I am not receiving any remuneration for participating in this study.

In case of queries during my study I may contact Elena Marie Mifsud – 79413924

Signature of participant _____

Name of participant_____ (*in block letters*)

ID number: _____

Signature of Chief Investigator _____

Name of Chief Investigator __ELENA MARIE MIFSUD__

ID number: _____400790M_____

DATE _____

PROPOSTA GĦALL-FORMULA TAL-KUNSENS

Jien/a ċittadin/a Malti/ja u għalaqt tmintax (18)-il sena.

Talbuni biex nieħu sehem fi studju riċerka:

Safer Anticoagulation Management in the Community: A Pharmacist-led Approach

L-għan u d-dettalji tal-istudju spjegathomli **Elena Marie Mifsud**

li ukoll iċċaratli xi mistoqsijiet li għamilt.

Nagħti kunses lil persuna responsabli għal din ir-riċerka biex tintervistani u tagħmel l-osservazzjonijiet/testijiet neċessarji jew it-tnejn jew tieħu l-kampjuni neċessarji. Jiena mgħarraf bl-inkonvenzji li dan jikkawza.

Jiena nifhem li r-riżultati ta'dan l-istudju jistgħu jintużaw għal skopijiet xjentifiċi u jista' jiġi ppubblikat rapport miktub: jekk isir hekk b'ebda mod ma nista' nkun identifikat/a, individwament jew bħala parti minn grupp, mingħajr il-kunsens tiegħi bil-miktub.

Jiena m'għandi l-ebda dmir li nieħu sehem f'dan l-istudju u dan qed nagħmlu minn rajja.

Jiena nista', meta rrid, ma nkomplix nieħu sehem fl-istudju, u mingħajr ma nagħti raġuni. Dan ma jaffetwa bl-ebda mod l-kura, l-attenzjoni u t-trattament li normalment jiġi mogħti lili.

Jiena mhux qed nitħallas biex nieħu sehem f'dan l-istudju.

Jekk ikolli xi diffikultà waqt l-istudju, nista' nsaqsi għal Elena Marie Mifsud - 79413924

Firma tal-parteċipant: _____

Isem tal-parteċipant: _____ (*b'ittri kbar*)

Numru tal-identità: _____

Firma tal-persuna responsabbli għal din ir-riċerka: _____

Isem tal-persuna responsabbli għal din ir-riċerka: ELENA MARIE MIFSUD

Numru tal-identità: 400790M

DATA _____

Appendix 5

Ethics approval

L-UNIVERSITÀ TA' MALTA
Msida - Malta
SKOLA MEDIKA
Sptar Mater Dei

UNIVERSITY OF MALTA
Msida - Malta
MEDICAL SCHOOL
Mater Dei Hospital

Ref No: **09/2016**

Friday 13th May 2016

Ms. Elena Marie Mifsud
39, Tarsus
Triq it-Torri tal-Kaptan
Naxxar

Dear Ms. Elena Marie Mifsud,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Safer Anticoagulation Management in the Community: A Pharmacist-led Approach

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

E-MAIL: umms@um.edu.mt WEB: www.um.edu.mt/ms

Appendix 6

DOCUMENT classification system

	Category	Subcategories	When to use it	Example
D	Drug Selection (DRPs associated with the choice of drug)	Duplication	When 2 drugs of the same therapeutic class are prescribed together, or when a patient is taking 2 different brands which contain same medication	Patient on perindopril and enalapril
		Drug interaction	When 2 drugs administered together cause a serious interaction	Interaction between paroxetine and warfarin increases risk of bleeding
		Wrong drug	Patient was prescribed or dispensed an incorrect medication	Patient who should be taking hydralazine being prescribed or dispensed hydroxyzine
		Incorrect strength	Patient was prescribed or dispensed an incorrect dose	Patient who should be taking simvastatin 40mg and was prescribed or dispensed simvastatin 20mg
		Inappropriate dosage form	The formulation of the medication does not match its intended use	Patient halving a film coated tablet, when the required dose exists
		Contraindications apparent	When a drug cannot be used in a patient due to their medical conditions or history	Patient suffering from heart failure being prescribed verapamil
		No indication apparent	Patient using a medication without a related indication	No clinical indication for the use of omperazole
		Other drug selection problem	Other dose selection problem that cannot be classified under another subcategory	

O	Over or underdose (DRPs associated with drug dosing)	Prescribed dose to high	Total daily dose of the medicine is too high for a particular patient or condition	Elderly women being prescribed digoxin 0.0625mg three times daily
		Prescribed dose to low	Total daily dose of the medicine is too low for a particular patient or condition	Adult patient being prescribed 1 puff daily of beclomethasone 50 micrograms inhaler daily
		Incorrect or unclear dosing instructions	The specified/prescribed dosing schedule is inappropriate	Warfarin prescription error which is not concordant with dose written on patient's anticoagulation booklet
		Other dose problems	Other dosing problem that cannot be classified under another subcategory	
C	Compliance (DRPs associated with medication administration and adherence)	Under-use by consumer	Patient is not taking all the prescribed doses	Patient not compliant with the daily administration of warfarin
		Over-use by consumer	Patient is taking extra medication than that prescribed	Patient overusing senna tablets
		Erratic use of medication	Patient taking medication on an erratic basis	Erratic use of diabetic medication, where patient decides to take medication according to what he eats
		Intentional drug misuse	Patient intentionally abusing of a medication	Patient claiming that the benzodiazepines dispensed were not sufficient
		Difficulty using dosage form	Patient finds it difficult to administer the medication due to its dosage form or difficulty in using device	Difficulty to administer inhalers
		Other compliance problem	Other compliance problem that cannot be classified under another subcategory	

U	Undertreated (DRPs associated with conditions that need to be managed)	Condition undertreated	Patient has a condition that is not being adequately treated	Patient suffering from HF and is not being prescribed a diuretic
		Condition untreated	Patient has a condition that is not being treated	Patient suffering from urine incontinence and is not taking any medication for the condition
		Prevention therapy required	Patient needs additional treatment to prevent side-effects	Patient on long term steroids and is not taking any calcium supplementation
		Other untreated indication problem	Other undertreated issues that cannot be classified under another subcategory	
M	Monitoring (DRPs associated with monitoring needs to ensure safe and efficient treatment)	Laboratory monitoring	To identify necessary laboratory tests to monitor the patient's conditions	Patient on medication that might alter liver function
		Non-laboratory monitoring	To identify necessary non-laboratory tests to monitor the patient's conditions	Patient requires regular blood pressure monitoring
		Other monitoring problem	Other monitoring problems that cannot be classified under another subcategory	
E	Education and Information (DRPs related with educational gaps and requests for information)	Consumer requests drug information	When patient asks for information on a particular medication	Patient requests information on the NOACs
		Consumer requests disease management advice	When patient asks for information on a particular disease or condition	Patient asks on infection prevention when using the catheters
		Other education or information problem	Other education related problems that cannot be classified under another subcategory	

N	Not classifiable	Clinical interventions that cannot be classified under another category	
T	Toxicity or adverse reaction	Toxicity, allergic reaction or adverse effect present	

Reproduced from: Pharmaceutical Society of Australia. Standard and guidelines for pharmacist performing clinical interventions [Internet]. Australia; 2011 [cited 2017 May 05]. Available from: http://www.psa.org.au/downloads/practice-guidelines/pharmacists-performing-clinical-interventions-guideline.pdf

Appendix 7

Medications causing drug-related problems

Table A10.1: Medications causing drug-related problems classified in 'Compliance' category (n=97)

Subcategory	Medication	Number of DRPs
Under-use by consumer	Warfarin	25
	Bumetanide	6
	All medicines	3
	Aspirin	2
	Simvastatin	2
	Valsartan	2
	Amiodarone	1
	Atenolol	1
	Bendroflumethiazide	1
	Digoxin	1
	Flecanide	1
	Glucosamine	1
	Lactulose	1
	Metformin	1
	Omeprazole	1
	Paroxetine	1
	Prednisolone	1
	Ranitidine	1
	Spironolactone	1
Other: Suboptimal timing of medication administration	Levothyroxine	7
	Warfarin	3
	Fluvastatin	2
	Glyceryl trinitrate patches	2
	Omeprazole	2
	Calcium	1
	Inhalers	1
Erratic use of medication	Celecoxib	2
	Omega 3	2
	All medicines	1
	Glucosamine	1
	Metformin	1
	Paracetamol	1
	Prednisolone	1
	Warfarin	1
Over-use by consumer	Warfarin	3
	Digoxin	1
	Senna	1
	Metformin	1
Other: Difficulty in changing warfarin dose	Warfarin	5
Intentional drug mis-use	Doxazosin	1
	Perindopril	1
Other: Patient non-compliant with INR testing	Warfarin	2
Difficulty in using dosage form	Inhalers	1

Table A10.2: Medications causing drug-related problems classified in 'Education' category (n=90)

Subcategory	Medication/Disease	Number of DRPs
Patient education to address certain gaps	Warfarin	72
Consumer requests drug information	NOACs	11
	Inhaler use	2
	Tacrolimus	1
	Sodium	1
	All medicines	1
Consumer requests disease management advice	Diabetes	1
	Infection	1

Table A10.3: Medications causing drug-related problems classified in 'Drug Selection' category (n=81)

Subcategory	Medication/Interaction	Number of DRPs
Drug interaction	Increase risk of bleeding	31
	Increase risk of bradycardia	16
	Increase risk of myopathy/rhabdomyolysis	6
	Increase risk of hyperkalaemia	6
	Increase risk of changes in QTC	2
	Increase risk of anticholinergic effects	1
	Increase risk of hypotension	1
No indication apparent	Omeprazole	8
	Omega 3	2
	Supplements	2
	Atorvastatin	1
	Bumetanide	1
Wrong drug	Clonazepam	1
Other: Duration of treatment: Review date for furosemide dose increments	Furosemide	1
Other: Need for treatment?	Catheterisation	1

Table A10.4: Medications causing drug-related problems classified in 'Toxicity and Adverse Reactions' category (n=19)

Subcategory	Medication	Number of DRPs
Adverse Reaction	Combination of antihypertensives	5
	Simvastatin	4
	Warfarin	3
	Amiodarone	1
	Amitriptyline	1
	Amlodipine	1
	Dutasteride and Tamsulosin	1
	Iron	1
	Perindopril	1
	Prochlorperazine	1

Appendix 8

Dissemination of results

Poster presented at the Maltese Cardiac Society Conference, October 2016

Safer Anticoagulation Management in the Community: A Pharmacist-Led Approach

Elena M. Mifsud[1], Francesca Wirth[1], Robert G. Xuereb[2], Christopher Barbara[3], Anthony Serracino-Inglott[1], Lilian M. Azzopardi[1]
1. Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
2. Department of Cardiology, Mater Dei Hospital, Msida, Malta
3. Department of Pathology, Mater Dei Hospital, Msida, Malta
email:emif0008@um.ed.mt

INTRODUCTION

Due to its narrow therapeutic margin, warfarin is recognised as a high-risk drug.[1] Anticoagulation clinics focus on determining the patient's INR value and on adjusting the dose of warfarin.[2] Inclusion of a pharmacist-led Medicine Use Review (MUR) service within an anticoagulation clinic allows for the development of an individualised pharmaceutical care plan to ensure treatment efficacy with the lowest likelihood of complications.[3]

AIMS

- To develop and implement a pharmacist-led clinical session for patients on warfarin.
- To perform a MUR for each patient and assess drug-related problems (DRPs) identified and type of interventions recommended.
- To assess patient's knowledge and level of adherence to warfarin treatment.

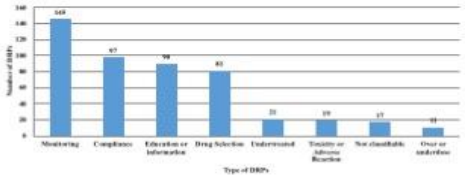
METHOD

- **Approval & Setting:** Following ethics approval, 100 patients taking warfarin were recruited by convenience sampling from 6 community pharmacies.
- **Psychometric evaluation:** Psychometric evaluation of the developed research tools, which included a patient questionnaire and medication use booklet, was performed using a two-round Delphi technique for validation and test-retest for reliability.
- **Pilot Study:** A pilot study was performed on 10 patients to test applicability and practicality of research tools and to analyse the clinical approach suggested.
- **Patient Recruitment:** Following informed written consent an appointment was set for all 100 patients to attend the structured pharmacist-led clinical session.
- **•Medication Reconciliation:** Patients provided the pharmacist with medical documents related to their anticoagulation control and health conditions.
- **Documentation:** Detailed patient medical and medication history was compiled in the developed medication use booklet.
- **•INR testing:** The POCT CoaguChek®XS (Roche Diagnostics) device was used to determine whether the patient's INR was within range and whether the patient requires a change in warfarin dose.
- **Medicine Use Review:** Comprehensive assessment of the compiled patient's medical information was performed to identify actual or potential DRPs, with special attention given to detection of issues which may affect the safety of warfarin use.
- **•Questionnaire:** Patient's knowledge and adherence to anticoagulation treatment was assessed using the designed questionnaire which also included a warfarin knowledge test and was performed as a semi-structured interview.
- **Pharmaceutical Care Plan:** The DRPs detected were classified using the DOCUMENT method[4] and recommendations for any actions, interventions or referrals to other healthcare professionals required were documented in the patient booklet.

RESULTS

- Out of the 100 patients, 56 were male and 44 were female with a mean age of 70.6 years (33-89 years) and taking an average of 6.32 medications daily (1-16).
- 40 patients had an INR result which was out of range and were referred for further monitoring.
- Only 25 of the patients obtained a pass score of 9 out of 12 in the warfarin knowledge test. A low mean score of 7.42 out of 12 was observed.
- 25 patients missed at least one warfarin dose in the two weeks prior to the session, while 4 patients were taking a warfarin dose different to that prescribed.
- A total of 481 DRPs (mean 4.81/patient) were identified, of which 40% were related to warfarin treatment. Figure 1. shows the type and frequency of the identified DRPs.

Figure 1. Type and Frequency of Identified DRPs (N=481)



- The most common identified DRPs were need for monitoring (30%), lack of compliance (20%) and need for patient education (19%).
- For each identified DRP a clinical intervention was suggested of which; 48.6% were referred to the patient's physician for consideration, 24.1% of the interventions were performed by the pharmacist and another 21% of the recommendations were discussed with the patient to comply with given advice.

CONCLUSION

A pharmacist-led MUR service helped to assess patient knowledge level on warfarin and risks to patient safety. The high incidence of DRPs, low level of patient knowledge on warfarin and non-compliance demonstrate the need for comprehensive patient assessment which is not limited to anticoagulation and is strongly recommended to improve treatment outcomes that could contribute to safer anticoagulation management in the primary care setting.

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PHARMACIST-LED MEDICINE USE REVIEW FOR PATIENTS ON WARFARIN

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INTRODUCTION

Anticoagulation clinics offering medicine use review (MUR) enable individualised patient assessment to check and balance drug-related problems (DRPs). Patients on warfarin are ideal candidates for MUR due to treatment complexity.[1]

AIMS

- To develop and evaluate the impact of a pharmacist-led MUR service for patients on warfarin
- To assess patient anticoagulation knowledge and adherence to warfarin

METHOD

Research tools
- A pre- and post-intervention questionnaire and an 'Anticoagulation and medication profile' were developed.
- Psychometric evaluation using a two-round Delphi technique for validation and the test-retest method for reliability was performed.

Patient recruitment
- Following ethics approval, 100 patients were recruited from 6 community pharmacies by convenience sampling.
- Patients were invited to attend for a MUR and a follow-up session.

MUR (Pre-intervention patient assessment)
- The pre-intervention questionnaire was completed as a semi-structured interview to assess patient anticoagulation knowledge level, warfarin adherence and patient perception on the proposed service.
- INR testing was performed with the CoaguChek®XS point-of-care testing device.

MUR (Medication reconciliation)
- The patient's medical history and medication history was documented.
- Medication reconciliation was carried out to identify any DRPs.
- Each DRP was classified according to the DOCUMENT[2] system and a clinical intervention was recommended.

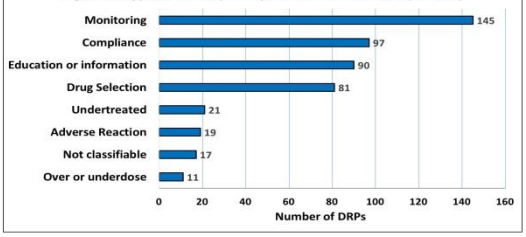
Follow-up
- Patients were re-assessed after 2 months.
- The post-intervention questionnaire was completed to assess the impact of the pharmacist intervention.
- Medication reconciliation was carried out to determine the degree of implementation of the clinical pharmacist's recommendations by the physician, community pharmacist and/or patient.

Data analysis
- IBM SPSS Statistics 24 was used to statistically analyse the data collected pre- and post-intervention to assess the impact of the pharmacist intervention.

RESULTS

- Hundred patients (56 male, 44 female, mean age 70.5 ±10.30 years) and taking an average of 6 ±2.76 medications daily were assessed.
- Forty patients had an INR result which was out-of-range.
- The mean score in the warfarin knowledge test improved from 7 out of 12 pre-intervention, to 10 out of 12 post-intervention ($p<0.05$).
- A significant improvement in adherence was observed post-intervention, where the number of patients non-adherent to warfarin decreased from 25 to 11 ($p<0.05$).
- A total of 481 DRPs (mean 4.57 ±1.83 DRPs/patient) were identified, of which 40% were related to warfarin treatment (Figure 1).

Figure 1.Type and frequency of identified DRPs (N=481)



- Eighty-four percent of the clinical pharmacist researcher's recommendations were accepted by the physician, community pharmacist or patient. The top accepted interventions resulted in 169 referrals for monitoring and 80 changes in treatment.
- Ninety patients were willing to start attending a pharmacist-led MUR clinic, if the service is implemented routinely.

CONCLUSION

The pharmacist-led MUR led to improvement in patient knowledge and patient adherence to treatment. The high proportion of implemented pharmacist recommendations demonstrate the contribution of the pharmacist intervention towards improving therapeutic outcomes. The willingness of patients to attend pharmacist-led MUR when implemented formally indicates the confidence of patients in clinical services offered by community pharmacists.

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Community Pharmacy - Pharmaceutical care

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Pharmacist-led medicine use review for patients on anticoagulation therapy

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Please specify your abstract type: Research abstract

Background and Objective: Patients on warfarin are ideal candidates for medicine use review (MUR) due to treatment complexity. The objectives were to develop and implement a pharmacist-led MUR for patients on warfarin, assess patient knowledge, adherence and INR control, address identified risks of treatment and evaluate patient perception of the service.

Setting and Method: Patients attended a structured MUR session with the clinical pharmacist researcher at a community pharmacy. A pre- and post-intervention questionnaire was administered as a semi-structured interview to assess patient knowledge, adherence and perception. INR testing was performed with the point-of-care (POC) CoaguChek®XS device. The Rosendaal linear interpolation method was used to calculate time in therapeutic range (TTR). Medication reconciliation was performed to identify DRPs and recommend clinical interventions. Follow-up was performed after two months to evaluate the impact of pharmacist intervention and degree of implementation of the clinical pharmacist researcher's recommendations by the physician, community pharmacist or patient.

Main outcome measures: Patient knowledge; adherence; INR control; DRPs; patient perception

Results: Hundred patients (56 male, 44 female; mean age 70.5 years; SD 10.30) were assessed. The mean knowledge score improved significantly post-intervention from 7 to 10, out of a maximum 12 points ($p<0.05$). A significant improvement in adherence was observed post-intervention, where the number of patients non-adherent to warfarin decreased from 25 to 11 ($p<0.05$). POC testing in the MUR session identified 40 patients with an INR outside the therapeutic range. TTR increased significantly from 69% to 80% post-intervention ($p<0.05$). A total of 632 medications were reconciled (mean 6/patient; SD 2.76) and 481 DRPs (mean 5/patient; SD 1.83) were identified, out of which 40% were related to warfarin. Need for monitoring (30%), lack of compliance (20%) and need for education (19%) were the top DRPs identified. Eighty-four percent of the recommendations were accepted. Ninety patients would be willing to attend for pharmacist-led MUR if the service is implemented routinely.

Conclusion: Improvement in patient knowledge, adherence, INR control and the high percentage of implemented recommendations suggest that pharmacist-led MUR improves therapeutic outcomes and patient safety. Patient satisfaction with the pharmacist's intervention suggests that patients are in favour of expansion of the clinical activities of community pharmacists through MUR.

Disclosure of Interest: None Declared