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**A Nurse-led Mobile Health Intervention to Promote
Cardiovascular Medication Adherence in a Cardiac
Rehabilitation Setting: a Pilot Feasibility Study**

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Degree of Doctor of Philosophy in Nursing Studies

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DECLARATION OF OWN WORK

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Assessed work: PhD Thesis

Title of work: A Nurse-led Mobile Health Intervention to Promote Cardiovascular Medication Adherence in a Cardiac Rehabilitation Setting: a Pilot Feasibility Study

I confirm that this thesis presented for the degree of Doctor of Philosophy in Nursing Studies, has

- i) been composed entirely by myself
- ii) been solely the result of my own work
- iii) not been submitted for any other degree or professional qualification

Signature Date

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ABSTRACT

Background - Mobile health (mHealth) interventions to promote medication adherence have shown promise; among patients primarily diagnosed with Coronary Heart Disease (CHD), however, there is a lack of evidence for nurse-led mHealth interventions, in this particular group in Iran.

Aim - To refine and evaluate a pre-developed nurse-led mHealth intervention to promote cardiovascular medication adherence in Iranian adult, male and female Cardiac Rehabilitation (CR) outpatients.

Methods - A quantitative-dominant mixed methods study was conducted drawing upon the Medical Research Council's (MRC) Framework on the development and evaluation of complex interventions. Phase 1 comprised of a self-completion CHD patients' survey (n=123) and three focus groups with cardiac nurses (n=23) within three public university-affiliated hospitals in Tehran, which in turn informed Phase 2 (the exploratory trial phase). The automated Short Message Service (SMS) medication reminder was designed based on the dimensions of adherence suggested by the World Health Organisation (WHO) and Bandura' Self-efficacy Theory. The intervention was refined according to the findings from Phase 1 and then piloted in an Iranian CR setting. Seventy eight CHD patients who were 18 years or older, and had mobile phone access were recruited and randomised to receive either daily SMS reminders (n=39) or usual care (n=39) for 12 weeks. The primary outcome was the effect on cardiovascular medication adherence as measured by the self-reported Morisky Medication Adherence Scale; secondary outcomes explored the feasibility of the mHealth intervention, intervention effect on medication adherence self-efficacy, cardiac ejection fraction, cardiac functional capacity, hospital readmission/death rate and health-related quality of life. Patient acceptability was assessed through completion of a post-intervention survey.

Results - Feasibility was evidenced by high ownership of mobile phones in CHD patients, high application of SMS messaging, positive patients' perception about the intervention, suboptimal cardiovascular medication adherence and patients' high interest in receiving SMS reminders for their medications. Participants in the intervention group showed higher self-reporting of medication adherence compared to the usual care group $\chi^2 (2) = 23.447$; $P < 0.001$. The Relative Risk (RR) was

indicated that it was 2.19 times more likely for the control group to be less adherent to their medications than the intervention group (RR = 2.19; 95% Confidence Interval (CI) 1.5 - 3.19). All secondary outcomes improved in the intervention group at the end of the study. Acceptability was evidenced by participants who received the intervention reporting that they perceived the SMS reminders useful.

Conclusion - The SMS medication reminder intervention was well accepted and feasible with significantly higher reporting of medication adherence in Iranian CHD patients. Effect sizes were established for use in future follow-up evaluations of the mHealth intervention.

LAY SUMMARY

There are some patients who require support to take their medication after leaving the hospital. Using text message reminders sent by healthcare staffs to patients' mobile phones may help them remember to take their medications after they have left the hospital. For patients in Iran who have heart disease, we do not know if nurses sending text message reminders to patients' phones to improve their medication taking is possible and if it works. In this study, we hoped to study these issues further.

We asked 123 patients with heart conditions to answer a series of questions about their thoughts on using mobile phones to remind them to take their medication and whether it was possible and acceptable to them. For example, we asked whether they owned a mobile phone and sent/ received text messages to/ from others. We also asked them their thoughts on being sent text message reminders, when and how often they would prefer to receive reminders. We also spoke with a total of 23 nurses who were caring for patients with heart conditions about their thoughts on text message reminders. Nurses stated that text messages would be useful and could potentially act as a medication reminder, create a connection from hospital to home and avoid negative outcomes of medication mismanagement. We used all information from patients' answers and nurses' opinions to design automated text message reminders. We then went to a hospital in Tehran and recruited 78 patients who attended one outpatient clinic called "Cardiac Rehabilitation" (an exercise programme after patients have recovered from a heart attack). We divided them randomly into two groups (39 patients in each group). One group received daily text message reminders on their mobile phones for 12 weeks and the other group received the usual care with no text reminders (this type of study is called a "trial"). Before introducing the text message reminders to the groups, we visited all patients and asked questions about their age and background, any difficulties they had with taking their medications, general health, physical and mental wellbeing. After 12 weeks, we visited all the patients again and asked similar questions about their medications and health to make a comparison. We also asked them to answer questions about their experience of receiving reminders for their heart medications.

Our results showed that most of the patients, who took part in the initial survey, reported owning a mobile phone, used text messaging regularly and were happy to receive text reminders because they had difficulty in taking their heart pills. In the trial after 12 weeks, patients who received text reminders took their medications more accurately and their health was improved compared to patients who did not receive it. Patients also were satisfied with text messaging and felt that it helped them to remember to take their heart medications.

Overall, nurse-led text message medication reminders were well accepted and helpful with greater results in medication taking in Iranian patients with heart disease. We also know that it is possible to use text message reminders in Iran. We now need to conduct a larger trial in future to understand more about the effect of text message reminders on a larger number of patients to see if we achieve similar results.

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GLOSSARY OF ACRONYMS

AA-Ag	Arachidonic Acid-induced platelet Aggregation
ACC	American College of Cardiology
ACEI/ARB	Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers
ACS	Acute Coronary Syndrom
AHA	American Heart Association
ART	Anti-Retroviral Therapy
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CASP	Critical Appraisal Skills Programme
CHD	Coronary Heart Disease
CI	Confidence Interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CMG	Continuous multiple-interval Medication Gap
CONSORT	Consolidated Standards of Reporting Trials
CR	Cardiac Rehabilitation
CSA	Continuous Single-interval Medication Availability
CVD	Cardiovascular Disease
EF	Ejection Fraction
eHealth	Electronic Health
EMR	Electronic Medical Records
ESC	European Society of Cardiology
EU	European Union
FC	Functional Capacity
FGD/ FGs	Focus Group Discussion/ Focus Groups
GDMT	Guideline Directed Medical Therapy
GP	General Practice
HbA1C	Haemoglobin A1C
HF	Heart Failure
HIV	Human Immunodeficiency Virus

HR-QOL	Health-related quality of life
ICD-10	International statistical Classification of Diseases and Related Health Problems (the 10th revision)
ICN	International Council of Nursing
ICT	Information and Communication Technology
IMB	Information Motivation Behavioural theory
IT	Information Technology
IVR	Interactive voice response
KP	Kaiser Permanente
LVEF	Left Ventricular Ejection Fraction
MA	Medication Adherence
MAGiC	Managing Access to Grey Literature Collections
MASE	Medication Adherence Self Efficacy
MCS	Mental Component Summary
MEDAS	Mediterranean Diet Adherence Screener
MEMS	Medication Event Monitoring System
mHealth	Mobile Health
MI	Myocardial Infarction
MMAS	Morisky Medication Adherence Scale
MPR	Medication Possession Ratio
MRC	Medical Research Council
NCCSDO	National Coordinating Centre for Service Delivery and Organisation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
NYHA	New York Heart Association
OR/ AOR	Odds Ratio/ Absolute Odds Ratio
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Summary
PDC	Proportion of Days Covered
PhD	Doctor of Philosophy
PICO	Patient, Intervention, Comparison and Outcome

RCT	Randomised Controlled Trial
RR	Relative Risk
SAS	Specific Activity Scale
S-CVI/Ave	Scale for Content Validity Index/ Average
SD	Standard Deviation
SF12V2	Short Form 12 item (version 2) Health Survey
SIM cards	Subscriber Identity Module cards
SMS	Short Message Service
SPSS	Statistical Package for the Social Sciences
STEMI	ST-Elevation Myocardial Infarction
TM	Text Message
UA	Unstable Angina
UK	United Kingdom
UNESCO	United Nations Educational, Scientific and Cultural Organisation
USA	United States of America
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

This introduction chapter is presented in eight sections that review the background information relating to Cardiovascular Disease (CVD), Cardiac Rehabilitation (CR), medication adherence among patients suffering from Coronary Heart Disease (CHD) and Mobile Health (mHealth). The first section provides an overview of the nature and prevalence of CVD in different regions in the world and in Iran, where this study will be conducted. In the second section, the role of CR programmes and their importance in secondary prevention of CVD will be presented. This chapter also provides the background and sets the scene regarding non-adherence among cardiovascular patients. mHealth as a new intervention to improve medication adherence will be introduced with a specific focus on CHD patients. Finally, the significance of the study and the structure of this thesis will be described.

1.1 Cardiovascular Disease

According to the World Health Organisation (WHO) (2016a), CVD is the main reason for mortality worldwide, accounting for more than 17 million deaths each year (46% of all deaths caused by non-communicable diseases) and this figure is projected to increase reaching 23.6 million by 2030. Over 80% of CVD deaths take place in low and middle-income countries (WHO, 2016a). CVD was the cause of an estimated 9.3 million deaths in the Asia/Pacific region and accounted for about one-third of all deaths in 2012 (WHO, 2016a). CVD prevention in Asia is an important issue for world health, because half of the world's population resides in Asia (United Nations Economic and Social Commission for Asia and the Pacific, 2016). CHD, the most important type of CVD, is manifested when the coronary arteries, become narrowed or blocked and cannot supply adequate blood to the heart; This can cause a heart attack, angina or heart failure (National Health Service, 2014). CHD accounts for 46% of cardiovascular deaths in male and 38% in female globally (Mendis et al., 2011). It alone caused approximately 380,000 death for both men and women (accounts for 1 in 6 deaths) every year in the United States (US) (Murphy et al., 2013). CHD causes nearly half of all deaths in Europe and 40% in the European Union (EU) (Nichols et al., 2014). It continues to be a major cause of mortality and morbidity in the United Kingdom (UK). It is responsible for around 160,000 deaths

per year in the UK (British Heart Foundation, 2015). Near 7 million people are living with cardiovascular disease in the UK: 3.5 million men and 3.5 million women (British Heart Foundation, 2015). In Asia the CHD-related mortality rate varies from 103 to 366 per 100000 adult populations (Wong et al., 2015). Although CHD is the most common cause of death in Asian communities, including Iran (the study setting), data on incidence of CHD is scarce in the Middle East population (Khalili et al., 2014). The Middle East and parts of Eastern Europe probably have the highest cardiovascular death rates in the world (Motlagh et al., 2009).

CHD accounts for nearly 50% of all deaths per year in Iran as a middle income country in the Middle East with a total population of over 76 million (World Health Organisation, 2014). This figure is similar to the mortality rate caused by cardiovascular disease in Turkey (47%) and Saudi Arabia (46%), neighbouring countries in the Middle East region (World Health Organisation, 2014). In Tehran, the largest city and the capital of Iran with a population of around 8.3 million, more than 40% of mortality has been related to CVD (Khalili et al., 2012). Approximately 20% of adults aged 30 years and over in this capital city have symptoms or signs of CHD (Hadaegh et al., 2009). According to a 10-year population-based cohort study, the crude CHD incidence rate in men was about twice that in women (11.9 vs. 6.5 per 1000 person-years) (Khalili et al., 2014). As a comparison, this incidence of CHD is lower than Northern Europe and higher than Southern Europe (Menotti et al., 2000). The incidence of CHD in East Asia during the last decade was much lower than that observed in the Iranian population; A study from China showed an age-standardised incidence of 2.2 in men and 1.2 in women per 1000 persons (Sun et al., 2012). Another study reported this finding for Japanese aged 40–69 years, equal to 1.0 and 1.8 per 1000 persons for men and women, respectively (Kitamura et al., 2008).

According to the Ministry of Health and Education of Iran, the majority of all CVD deaths are attributable to CHD; therefore a policy priority and the long-term goal will be the reduction of 25% in cardiovascular mortality rate in the next 10 years (Ministry of Health and Education of Iran, 2016).

High prevalence of and a predicted large rise in cardiovascular disease over the coming decades, provide the rationale for targeted interventions and experimental

studies on primary and secondary cardiovascular prevention. This may help to reduce cardiovascular event rates, and should assist in managing the impact of future CVD.

1.1.1 Impact of Cardiovascular Disease

Cardiovascular disease has been considered an epidemic chronic condition at present and was predicted to remain the single most important disease in the world in the terms of mortality, morbidity, disability and economic loss until the year 2020 (WHO, 2016). In the US, despite population-based prevention programmes over previous decades, CHD remains the leading cause of death and early and permanent disability (Go et al., 2014). It also has an adverse impact on quality of life (Jneid et al., 2012). In spite of the lack of high-quality data, it can be clearly seen that CHD is by far the most significant public health issue across Asia and the Middle East, an issue that may reach catastrophic prevalence unless confronted efficiently (Ramahi, 2010). CHD is associated with tremendous morbidity, societal health problem, stress, high expense of care, and increased financial burden due to loss of productivity (World Health Organisation, 2013).

Middle Eastern countries have mostly young populations that are at high risk of CHD as a result of uncontrolled tobacco smoking and inactive stressful urbanised lifestyle and unhealthy eating habits (World Health Organisation, 2016b). The oil industry is the main source of income in Iran. Prevention of the financial burden caused by CHD is of importance to preserve a productive workforce. According to a study, 65% of CHD patients that were admitted to the National Iranian Oil Corporation (NIOC) Central Hospital in 1999–2000 were in their most productive years of life, between 40 and 55 years old (Larijani et al., 2003). In some Middle East countries, obesity, diabetes mellitus, hypertension and lipid disorders are on the rise as a consequence of rapid economic growth and increasing urbanisation (Teo et al., 2013). An Iranian population-based study showed that well-known modifiable risk factors, as the essential preventable parameters of causal diagram for CHD, contribute to about 40% and 50% of the CHD risk in men and women, respectively (Khalili et al., 2014). The absolute consequence is high prevalence of CVD risk factors in large young populations with limited access to prevention strategies and facing inadequate and poorly financed healthcare systems. These currently unsustainable healthcare systems will be expected to provide expensive secondary

and tertiary health care to elderly people with very high prevalence of CVD in future (Ramahi, 2010).

Poor adherence to medications and health recommendations among cardiovascular patients is an additional risk factor contributing to the progression of disease, complications, rehospitalisation, reduced quality of life, higher morbidity and mortality and healthcare expenses (Munger et al., 2007, Piepoli et al., 2016).

Throwing light on the impact of CHD provides the foundation for the development of interventions aimed at primary and secondary prevention of CHD. Secondary prevention such as Cardiac Rehabilitation (CR) contains intensive control of risk factors, drug treatment, and follow-up visits that play a major role in preventing recurrences of CHD and its complications (Achtien et al., 2013, Piepoli et al., 2016).

1.2 Cardiac Rehabilitation (CR)

CR is an essential part of CHD care recommended by international guidelines such as the American Heart Association (2013), the American College of Cardiology (2011), the European Society of Cardiology (2016) and the British Association for Cardiac Rehabilitation (2017) that includes physical, education and psychological input focusing on health and life-style behaviour change, risk factor modification, and psychosocial well-being.

CR as a secondary prevention programme plays an important role among non-pharmacological interventions to reduce the risk of cardiac recurrence and risk factor modifications (Cossette et al., 2012). CR is one of the most cost-effective and multidisciplinary disease management service consisting of making required changes in lifestyle and appropriate use of medications that assist patients to slow or even reverse the development of coronary disease (Anderson et al., 2016, British Heart Foundation, 2016). The main goals of CR are to help patients improve both physically and psychologically after a cardiac event and decrease the risk for recurrent cardiac events (Achtien et al., 2013). Patients who participate in CR have a 20% relative decrease in cardiac mortality over the following 5 years (Mampuya, 2012).

CR should be available as a coherent package of exercise, education, medications and psychological support and as an integrated approach within

secondary prevention services (British Heart Foundation, 2016). While extensive research and clinical guidelines support the role of pharmacological treatment and the importance of medication adherence, within the secondary prevention of CHD these seem a neglected component of the CR programme (Jneid et al., 2012, O'Gara et al., 2013, Park et al., 2013).

1.2.1 Phases of Cardiac Rehabilitation

Current clinical British guidelines recommend that it is necessary for all CHD patients to receive secondary prevention to maximise physical, psychological and societal wellbeing (British Heart Foundation, 2016, National Institute for Health and Clinical Excellence, 2013, Piepoli et al., 2016). The healthcare system in Iran aims to follow current clinical guidelines and provide quality CR services for cardiac patients (Sarrafzadegan et al., 2007). CR is commonly divided into either three or four phases, with the content of these phases varying between nations (Price et al., 2016). CR in Iran includes three phases with different components adapted from American Heart Association (2013) and the American College of Cardiology guidelines (2011): inpatient recovery period in the cardiac intensive care unit (Phase I), exercise programme in outpatient CR clinic (Phase II), and finally long-term follow-up or ongoing prevention (Phase III) (see Table 1.1). CR teams generally comprise of cardiologists, cardiac rehabilitation nurses, physiotherapists, nutritionists and psychologists (Moghadam et al., 2008, Sharif et al., 2012). The programme follows progression from hospitalisation after an acute event through to recovery and ongoing maintenance where CR is part of the post cardiac event process. Table 1.1 outlines the phases of CR currently in place in Iran.

Table 1.1. Description of CR phases in Iran (Moghadam et al., 2008, Sharif et al., 2012)

CR Phases	Description
Phase I	It occurs before hospital discharge or inpatient stage or after a 'step change' in the patients' cardiac condition includes medical assessment, verbal and written self-help advice and education, risk factor assessment, medication prescription, mobilisation and discharge planning with involvement of partner or family.
Phase II	It occurs after four to six weeks of an acute cardiac event, involves supervised and structured exercise training in combination with educational and psychological support and advice on risk factors. At the first session of this phase, patients receive specific education to reduce cardiac misconceptions and encourage smoking cessation and weight management; vocational advice and rehabilitation to assist return to work or retirement; and referral to a psychologist, cardiologist, or exercise physiologist.

CR Phases	Description
Phase III	It includes the long-term maintenance of changed behaviour. Involvement with a local cardiac support group, which involves exercise in a community centre such as a gym or leisure centre, may help maintain physical activity and lifestyle change.

1.3 Medication Adherence

This section describes the concept of medication adherence and reviews the literature around its terminology, different types of medication non-adherence and measurement strategies. Prevalence and background information relating to medication non-adherence are discussed with a specific focus on cardiovascular medications. Important factors that have an impact on patient medication non-adherence are considered. Influencing factors related to non-adherence, characteristics of diseases, and aspects of the healthcare setting that may impact on patient's non-adherence are presented.

1.3.1 Medication Adherence Terminology

Different terminologies exist and are used interchangeably to explain the way prescribed medications are taken or not taken by patients. The concept of adherence has been defined by the WHO (2003, p3) as:

“The extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”

This definition emphasises clearly the active role of the patient in their treatment regimen and also requires patient's agreement on the recommendations. Therefore, effective communication and interaction between patient and health professional is crucial.

While the constructs of adherence and compliance have been used interchangeably in many conditions, each term definition is quite different; adherence includes the patient's acceptance with the recommended therapies, in contrast compliance indicates patients' passiveness. Compliance is a concept that implies patients' dependency and exaggerates power of physician on patients in the treatment process. Adherence puts nurses and other care providers in partnership with their patients in improving health outcomes (Gould and Mitty, 2010). In the present study, the term “adherence” is used to refer specifically to patient's medication taking behaviour.

1.3.2 Medication Adherence Measurement

In current practice, there is no “gold standard” for evaluating medication adherence behaviour and it remains a challenging issue (Lehmann et al., 2014, McGinnis et al., 2014). When choosing a method of adherence measurement, the practicality and reliability of the method should be considered (Stewart et al., 2014). Adherence measurement approaches can be divided in two direct and indirect methods of measurement:

Direct Methods

Direct methods of medication adherence measurement are less common and refer to the detection of a metabolite or marker in patients’ blood. This measurement strategy is not without drawbacks since a variety of individual factors such as diet, herbal treatments, drinking caffeinated beverages or alcohol, taking vitamins, pregnancy and intensive exercise can lead to misleading findings. In addition such methods are often impractical, costly and invasive (Stewart et al., 2014).

Indirect Methods

The most common indirect method of medication adherence measurement is patient’s self-report using validated scales, however it has been proposed that patients tend to report their behaviour inaccurately or cannot remember previous medication consumption, these can therefore distort the results (Berben et al., 2011, Stirratt et al., 2015). Other indirect measurements could be implemented based on a pill count strategy that refers to counting the number of remaining pills left in the patient’s medication container (Stirratt et al., 2015). Although this is a simple method, it can also be unreliable; the patients in order to appear adherent to medications can change medicines between bottles or throw them out before checks are made (Stewart et al., 2014). Counting inaccuracies can also lead to overestimation (Brown et al., 2016). Among other approaches, electronic monitoring devices like the Medication Event Monitoring System (MEMS) are an innovative approach which records the time and date of each opening/closing of the medication container (Jose and Jimmy, 2011). However, it is an expensive device and is not practical to use widely (Lehmann et al., 2014, Jose and Jimmy, 2011). Alternatively, a pharmacy database can be used to see if the patient is (re)filling the initial prescription in future. The main problem with this approach is that patients may use

other pharmacies to refill their medications (Stewart et al., 2014). In the present study, it was not possible to use the MEMS and pharmacy database as to the knowledge of the researcher, such electronic monitoring devices for medication taking and electronic pharmacy claim data were not available in Iran during the time of this study. Likewise, there were cost constraints.

According to the literature, triangulation of approaches that combine practical self-report measurement and reasonable objective methods could be an effective way to measure medication adherence behaviour and increase the reliability and validity of the measurement (Brown et al., 2016, Lehmann et al., 2014, Osterberg and Blaschke, 2005, Stewart et al., 2014).

1.3.3 Reasons for Medication Non-adherence

According to the WHO Multi-dimensional Adherence Model (2003), medication non-adherence is a multi-factorial issue (see Section 2.4). Poor adherence to medications can be attributed to both intentional and/or non-intentional reasons (Berben et al., 2011, Brown et al., 2016). Intentional non-adherence is an active process whereby the patient chooses to deviate from the treatment regimen (Brown et al., 2016, Gadkari and McHorney, 2012). This may be a rational decision process in which the individual weighs the risk and benefits of treatment against any adverse effects (Brown et al., 2016). Unintentional non-adherence is a passive process in which the patient may be careless or forgetful about adhering to the treatment regimen; almost half of the medication non-adherence is unintentional or due to forgetfulness, carelessness, complexity of the treatment regimen, problems of accessibility, cost and competing life demands (Brown et al., 2016, Gadkari and McHorney, 2012). Intentional non-adherence is viewed as being related to people's beliefs about their therapy, illness, prognosis and their expectations towards medication consumption (Brown et al., 2016, Osterberg and Blaschke, 2005).

Based on the Multi-dimensional Adherence Model (2003), the WHO proposes that adherence results from the interplay of five sets of factors (dimensions) including socioeconomic, therapy, condition, healthcare team/ system, and patient-related factors (see Section 2.4).

Being aware of reasons related to medication non-adherence helps provide an understanding of the effectiveness of adherence interventions on perceived and

actual medication use, barriers, adherence levels, and consequently patient outcomes (Berben et al., 2011, Brown et al., 2016). To be more precise, appropriate adherence interventions should address multiple barriers to medication adherence (Boswell et al., 2012, Brown et al., 2016, Kardas et al., 2013).

1.3.4 Nurses' Role in Improving Medication Adherence

It has been evidenced in the literature that nurses are well placed to provide adherence care and follow-up for discharged patients since they are present in all healthcare settings and have a close relationship with patients (Linn et al., 2014, Najafi et al., 2016, Neubeck et al., 2011, Simoni et al., 2011, Souza-Junior et al., 2016, Van Camp et al., 2013). Through effective communication skills they will be able to provide valuable information as well as support for patients and their families throughout their journey from acute care to secondary prevention (Najafi et al., 2016, Van Camp et al., 2013). In this way, patients demonstrate higher levels of adherence when they are provided with care and support by the same healthcare professional over time (Van Camp et al., 2013).

The early phase of discharge from the hospital is a critical time when many patients discontinue medications and ongoing nursing interventions that affect adherence early can improve long-term health outcomes (Albert, 2008). Nurses should take an active role in assessment, education, care planning, and strategic implementation efforts that support patients' optimal self-care behaviours and promote medication adherence (Brown et al., 2016). It has also been advised by the Nursing and Health Policy Consultant of the International Council of Nursing (ICN) that nurses should provide a link and support through innovative approaches after discharge that scale up medication adherence and provide helpful information including accurate dosage, routes and frequency pattern of medications as well as the importance of maintaining adherence to treatment regimen (Sabaté, 2003). However, they currently act as disregarded and underused providers in optimising adherence and care outcomes (Van Camp et al., 2013).

A previous systematic review on interventions to enhance adherence to medication among patients with several chronic diseases reported interventions were largely pharmacist-delivered and were found to be ineffective (Williams et al., 2008). In contrast, another systematic review and meta-analysis of 10 Randomised Control

Trial (RCT) to evaluate the effect of nurse-led interventions on chronic medication adherence found that nurse-delivered methods were successful in improving adherence (Van Camp et al., 2013). These indicate that nurses can play an important role in promoting medication adherence and hence evidence-based nurse-led approaches should be added to other adherence support strategies in combination with the strengths and experience of other clinicians (Brown et al., 2016, Stolic et al., 2010, Van Camp et al., 2013).

1.3.5 Overview of Medication Non-adherence

Poor medication adherence is a complex and prevalent issue among patients that has not been sufficiently addressed (Brown et al., 2016, Santo et al., 2016). Long-term therapy among chronic patients that is mostly associated with multiple drugs prescription indicates an unsatisfying average adherence level of 50% in developed countries (Kyanko et al., 2013, Chisholm-Burns and Spivey, 2012). Findings from the REACH Registry, a large study in which 69,055 cardiovascular patients were recruited from 44 countries worldwide and followed up for four years, showed that only 48.6% were fully adherent to cardio-protective medications including anti-platelet, statins, and antihypertensive agents (Rodriguez et al., 2013). According to this study, greater adherence was observed in North America and Europe, whereas participants from Latin America and Asia had lower adherence level to their medications. In the PREMIER study that examined the rates of cardio-protective medication therapy discontinuation among multi-centre prospective cohort of 2498 patients experienced acute MI, it was found that more than 1 in 5 patients stopped taking aspirin, β -blockers, or statins and 1 in 8 stopped taking all three medications within one month after MI (Ho et al., 2006). Similarly, reports of poor adherence level have been identified in other conditions such as asthma (Petrie et al., 2012), diabetes, dyslipidaemia and Human Immunodeficiency Virus (HIV) (Van Camp et al., 2013, Langley and Bush, 2014).

Non-adherence to prescribed drugs contribute to an estimated annual cost of £230 million to the UK health care system (National Collaborating Centre for Primary Care, 2009). Similarly, in the US non-adherence issue costs \$100 billion each year (National Community Pharmacists Association, 2013). A study aimed at exploring the measures, reasons and expenses of poor use of medications identified

that improving levels of adherence could potentially save around £500 million in health-related costs (Trueman et al., 2010). NICE (National Institute for Health and Care Excellence) (2013), AHA (American Heart Association) (2013), ACC (American College of Cardiology) (2011) and ESC (European Society of Cardiology) (2012) clinical guidelines recommend optimisation of drug therapies for secondary prevention in cardiovascular patients. There are limited data related to the prevalence of medication non-adherence from developing countries, although its prevalence in these countries is 2 times greater compared to that reported from developed countries (Awad et al., 2017). In Saudi Arabia and other Gulf countries, mean medication wastage, in terms of the amount of medication products, was estimated to be near 26% and 42%, respectively and on the basis of medication costs, was around 20% in Saudi Arabia and 25% in other Gulf regions (Abou-Auda, 2003, Moradi-Lakeh et al., 2016).

In Iran, around 8,300 independent community pharmacies provide pharmaceutical services (Ministry of Health and Medical Education of Iran, 2014). Typically, urban Iranians consume 339 unit doses of medicines yearly (Zargarzadeh et al., 2005). Approximately 85% of the population has access to essential drugs and health insurance (Cheraghali et al., 2003, Zargarzadeh et al., 2007). Insurance coverage usually includes all drugs except vitamins, hygiene products, and selected imported medications not on the national formulary list. Patients pay about 30% of the prescription cost as a co-payment, and the rest is paid by the insurance company (Zargarzadeh et al., 2007). In terms of medication adherence, only 46.3% of Iranian families completed the entire course of medication prescribed by their physicians (Zargarzadeh et al., 2007). This number was similar in Saudi Arabia and Gulf countries at 32.7% and 43.7%, respectively (Abou-Auda, 2003, Moradi-Lakeh et al., 2016).

According to a previous systematic review of studies conducted in developing countries, pooled cardiovascular medication adherence was found to be minimal (equal to 57.5%) that is comparable to that reported for developed countries (equal to 50%) (Bowry et al., 2011). Therefore, many nations including Iran, are seeking ways to address medication non-adherence, which is an important modifiable cause of complications occurring in long-term conditions (Awad et al., 2017, Sarayani et al.,

2013). Poor medication adherence can lead to a suboptimal clinical advantage and health outcomes and is of significant concern in public health, in terms of quality of patients' lives and health costs (Van Camp et al., 2013). The results of enhanced medication adherence are, decreased rate of death and co-morbid problems, reduced re-hospitalisation and physician visits, higher life satisfaction and saved more health system expenses (Osterberg and Blaschke, 2005, Sarayani et al., 2013, Stevens, 2015).

Medication non-adherence is prevalent after hospital discharge among cardiac patients since many of the medications are titrated based on their effect on the patient's vital signs for optimal mortality benefit during the period in which the patient is undergoing CR (National Institute for Health and Care Excellence, 2013, O'Gara et al., 2013, Piepoli et al., 2016, Price et al., 2016). Moreover, the primary issue of how this group of patients familiarise themselves to their changing medications remains and it demands the implementation of adherence optimising interventions (Berben et al., 2011, White et al., 2013). In Iran, in addition to structured exercise, the first session of outpatient CR programme involves delivering information on various topics including medications in a group setting, presenting by a physician both verbally and in written form (Moghadam et al., 2008). However, evidence reported that educational interventions do not efficiently increase medication adherence and no significant differences were found in medication adherence following interventions presenting written information about medication compared to those that did not (Berben et al., 2011, Conn et al., 2009). In light of the complex and changing medication regimens, it would be more effective to focus on implementing alternatives to educational interventions especially using innovative approaches to improve adherence to cardiovascular medications in the process of CR (Gandapur et al., 2016, Pfaeffli Dale et al., 2015, Berben et al., 2011, Conn et al., 2009).

1.4 Electronic Health (eHealth)

The eHealth (also called digital health) encompasses an extensive area within healthcare management. The WHO (2016, p. 5) defined eHealth as:

“The cost-effective and secure use of Information Communication Technology (ICT) in support of health and health-related fields, including health-care services,

health surveillance, health literature, and health education, knowledge and research”.

The term eHealth is interchangeably used in various contexts to refer to health informatics, health information systems, health information technology, telehealth (i.e. an expansion of telemedicine), and medical informatics that come from several disciplines including information technology, computer science, health, and business (Sharifi et al., 2013).

eHealth also includes a comprehensive range of information systems in health care, such as patients electronic health records, payment (ePayment) and billing (eBilling) information, healthcare workers and hospital information, electronic prescription and innovations in health care and delivery of quality care (Park, 2011a). All operational daily tasks as well as decision and management systems can be handled by using eHealth to its full potential; in the other word, eHealth has the potential to facilitate mobile health, telemedicine, and other associated activities (Park, 2011a, Sharifi et al., 2013).

The growing application of eHealth delivers a variety of advantages that this promising innovation brings to health care that can be classified into different categories: clinical, financial, technical, organisational, professional, and patient-related benefits; the major advantages include reduction in operational expenses, rationalisation and high visibility of projects, prevention of fraud, online authorisation, availability of data, coordination of health service delivery, and privacy protection of data (Sharifi et al., 2013). Although eHealth provides health care with promising benefits, it has been less developed in comparison with other fields. According to Jordan et al. (2009), major barriers to a successful and sustainable eHealth implementation in almost all regions can be categorised into political, social, organisational and technical challenges. There is evidence that poor standardisation related to eHealth applications as well as financial issues, training expenses, and the diversity of platforms are main issues that have an association with failures or unsustainable eHealth implementations (Jordan et al., 2009, Mushtaq and Hall, 2009, Sharifi et al., 2013).

According to Sharifi et al. (2013), eHealth in Iran has been initiated since medical laboratories began to auto-analyse medical kits and provide a printed copy of the results for the patients. At that time, the most common storage device in

healthcare offices was 5.25-inch floppy disk. Then, in the mid-1990s, the first domestic software packages were developed in several hospitals to provide storage data from patient registration to discharge. At the end of the 1990s, the Social Security Organisation equipped its own healthcare centres with informatics technology including Health Level 7 (i.e. a framework for the exchange, integration, sharing, and recovery of electronic health information) and Electronic Data Interchange for Administration, Commerce and Transport standards. During the first decade of 2000s, various projects were initiated such as customisation of open source standard based on Iranian healthcare needs, the strategic ICT plan for the Iranian National Health (its local name is the TAKFAB plan for patients' electronic health records), development and implementation of a software application for cancer records in hospitals, and finally pharmacies' computerisation. Moreover, some eHealth pilot projects have been initiated in small-scale and the ICD-10 (i.e. the 10th revision of the International Statistical Classification of Diseases and Related Health Problems) was introduced to medical centres in order to record patients' health information. Although the Iranian health organisations were supplied with required hardware and communication infrastructure, the Electronic Health Records (EHRs) needs to be defined, clarified and integrated into hospitals information systems by the Ministry of Health and Medical Education. This includes the development of a long-term plan to gather and record health-related information of Iranian people, that is still in its initial stages.

1.5 Mobile Health (mHealth)

Mobile Health (mHealth) is a sub-segment of eHealth that is defined by the WHO (2011) as:

“Medical and public health practice supported by mobile technologies such as mobile phones and patient monitoring devices, personal digital assistants (PDAs), and other wireless devices” (World Health Organisation, 2011, p.6).

While mHealth interventions are reported to be used in higher-income countries (World Health Organisation, 2011), there is evidence to support/report the application of mobile technologies in lower-income countries (Blaya et al., 2010, Leach-Lemens, 2009). 95% of countries in the world have mobile phone networks with more mobile phone than landline subscriptions (Cole-Lewis and Kershaw,

2010). mHealth has been used because it offers interactive communication, which provides a wide range of opportunities from improving self-monitoring for those with chronic diseases to facilitate remote access to data and health records in rural areas (Cole-Lewis and Kershaw, 2010, World Health Organisation, 2011). mHealth innovations have been developed that address a range of issues such as improving the convenience, speed, and accuracy of diagnostic tests; monitoring chronic conditions, medication adherence, appointment keeping, medical test result delivery; improving patient-provider communication, health information communication, remote diagnosis, data collection, disease and emergency tracking and access to health records (Adler, 2007, Leach-Lemens, 2009). It has been reported that the use of technology as a remote intervention can lead to a 20% reduction in emergency admissions, a 14% reduction in hospital length of stay and a 45% reduction in mortality rates (Groupe Speciale Mobile, 2012).

mHealth is a rapidly expanding area of research and practice that is applied to a range of functions from support systems of clinical decision making and tools of data collection for healthcare professionals (Blaya et al., 2010, Lindquist et al., 2008), to providing support for health behaviour change and chronic disease management by patients in the community (Cole-Lewis and Kershaw, 2010). Text messaging, the most popular form of mHealth, can contribute to health behaviour change since it provides prompt and personalised patient-provider interaction and positive health reinforcement through regular reminders (Cole-Lewis and Kershaw, 2010, Fjeldsoe et al., 2009, Wei et al., 2011). mHealth, the use of mobile technology and Short Message Service (SMS) text messaging, is purported to be both cost-effective and feasible, thereby having the potential to ease continuing engagement post-hospitalisation for skilled nursing care (Gephart and Effken, 2013). Nurses, in their supporting role, can provide the link between physicians, other healthcare providers, and patients; they therefore have a pivotal role in the post-discharge follow-up care. Follow-up with patients can be ensured by implementation of evidence-based innovative tele-nursing approaches using mobile phone (mHealth) interventions in different conditions and settings such as follow-up of medication adherence among CHD patients in a CR setting. mHealth also has the potential to overcome the issue of patients' nonattendance in all sessions of hospital-based CR in Iran, as it can be

delivered anywhere and at any time. Whether a CHD patient is trying to adhere to a complex medication regimen, nurse-led mHealth approaches may provide support for them.

1.6 Description of the Previous Small-Scale Study

This PhD study developed and extended ideas from a small-scale evaluation of mHealth SMS reminder intervention in patients after hospital discharge following Acute Coronary Syndrome (ACS) (Khonsari et al., 2015). The main researcher (SKh) developed a text-messaging web-based software for her Master's research and conducted a pilot Randomised Controlled Trial (RCT) at a tertiary hospital in Malaysia. A total of 62 ACS patients were recruited and equally randomised to receive either automated SMS reminders before every intake of cardiovascular medications or only usual care within 8 weeks after discharge. The study showed that automated SMS reminders have the potential to improve cardiovascular medication adherence among Malaysian patients during the early post-discharge period.

There are some distinctions between the previous and current study both theoretically and methodologically (see Section 5.1).

1.7 Significance of the Study

Patients who have recently experienced a cardiovascular event are often discharged from the hospital with multiple new cardioprotective drugs including anti-platelet, lipid-lowering, beta-blocker and anti-angina agents (Scottish Intercollegiate Guidelines Network, 2013). According to international guidelines, all CHD patients should be offered secondary prevention and a CR programme. During the period of CR, many of the prescribed medications are titrated for optimal therapy (Packard et al., 2012). Cardio-protective drugs are important in the management of cardiac conditions as part of the preparation for physical activity and exercise programmes (The British Association for Cardiovascular Prevention and Rehabilitation, 2012). Considering the complexity of changing treatment regimens, a nurse-led mobile health intervention may have the potential to play an effective role in promoting adherence to cardio-protective medications among CHD patients during outpatient CR programme.

The potential for mobile phone use in health care is currently being defined; it also remains a significant opportunity for future research (Anglada-Martinez et al., 2015, Gandapur et al., 2016, Kay, 2011). The use of mobile technology to enhance medication adherence exclusively for patients with CHD has not been thoroughly investigated to date. Furthermore, few researches have been published to date about mHealth interventions to promote medication adherence specifically among patients who are recruited in the particular setting of CR in Iran.

The primary intervention for this study is based on the principles of Multidimensional Adherence Model adapted from the WHO (2003) and the principles of the Bandura's Self-efficacy Theory (1982) (see Chapter Two). The WHO model includes interactions between five sets of factors or "dimensions" including: social and economic factors, healthcare team- and system-related factors, condition-related factors, therapy-related factors and patient-related factors which ultimately affect patient outcomes. According to the Bandura's Self-efficacy Theory, perceived self-efficacy is determined as the most important component in behaviour change (Bandura, 2002) and has been examined in different areas of health behaviour change such as self-management of chronic conditions and medication adherence. In this study, the automated SMS intervention may promote self-efficacy through sending medication reminders, serve as a form of social support, and address factors related to the most important dimensions of the WHO Adherence Model, such as healthcare system- and patient-related factors to enhance cardiovascular medication adherence during the first months of CHD post-discharge in parallel with outpatient CR programme.

The Medical Research Council (MRC) framework provides a comprehensive and circular process for intervention development and evaluation (Senn et al., 2013). The present mixed-methods study comprised of two phases (preclinical phase and exploratory phase) guided by the MRC framework (2013). Using this framework helped to refine the previously developed mHealth intervention (from the Master's work) in order to make it appropriate to the Iranian context and conduct a pilot feasibility trial to evaluate the potential effect of the intervention on medication adherence among Iranian CHD patients.

1.8 Structure of the Thesis

This thesis is divided into seven chapters as below:

- Chapter One is the general introduction of this study and reviews the problems of CHD and medication non-adherence, role of nurses in improving patients' medication adherence as well as the potential for mobile phone technology (mHealth) to help address the non-adherence issue. Significance of the study and the structure of this thesis are presented at the end of Chapter one.
- Chapter Two reviews and critiques the existing theories and their relevance to the issue of long-term medication adherence. The theoretical frameworks used as a guide in this study including the WHO Multi-dimensional Adherence Model and The Bandura's Self-efficacy Theory are described, as well.
- Chapter Three is a critique of the evidence base presented as a literature review with a specific focus on interventions that have been implemented to address medication non-adherence in a variety of settings, conditions, and populations.
- Chapter Four describes aim and objectives, operational definition, study variables and the research methodology.
- Chapter Five provides descriptions about the research design, rationale for the chosen mixed-methods design, research process, details of data collection and data analysis along with the ethical considerations.
- Chapter Six presents the results of this research, according to each study objective.
- Chapter Seven provides the discussions of the findings and a comparison with existing literature. Implications for practice, study limitations and the research conclusion are presented, as well.

CHAPTER 2: CONCEPTUAL FRAMEWORK

Conceptual models may contribute to the design of interventions in various ways: by enhancing an understanding of health issue, guiding research and assisting the progress of transferring an intervention from a health issue, population and setting to another one (Bandura, 2012, Davis et al., 2015, Eccles et al., 2005). Therefore, this Chapter includes a short description of theories related to medication adherence and rationale for choosing the Self-efficacy Theory and the World Health Organisation (WHO) Multi-dimensional Adherence Model as frameworks to draw upon and inform the study intervention.

Leventhal et al. (1987) identified five major theoretical frameworks including Biomedical model; Rational belief theory; Communications approach; Self-regulative systems theory; and Social learning theories that can be used to guide medication adherence research. These theories are located particularly within the concept of adherence to long-term medication; This Chapter explains the main features of these theoretical frameworks; and discusses their relevance and appropriateness with regards to the study intervention and adherence to long-term medication for cardiovascular patients. The empirical evidence supporting the link between conceptual models and adherence behaviour change are also discussed.

2.1 Five Major Theories of Adherence

In terms of the issue of medication non-adherence, interventions have been developed to address the problem, but few of them explain their development processes, in particular using a theoretical framework (Munro et al., 2007). There are different psychological theories explaining behaviour change, causing challenges when selecting the most relevant one when attempting to understand that behaviour change within the context of the intervention being developed, implemented and evaluated. This is a significant consideration in evaluating existing theories to identify their relevance to long-term medication adherence, where the non-adherence consequences may be serious (Munro et al., 2007).

Five major theoretical perspectives related to adherence were identified from the literature:

1. Biomedical model;
2. Communications model;
3. Rational belief (cognitive) models;
4. Self-regulation models; and
5. Behavioural (Social-cognitive) models.

Reviewing health behaviour theories may help shed light on the processes underlying behaviour change. Therefore, the following sections review the most commonly used behaviour change theories applicable to long-term treatment adherence. The characteristics, limitations and implications of each theory in predicting behaviour and developing an intervention to promote adherence behaviour are discussed.

2.1.1 Biomedical Model

The Biomedical model of disease proposed by Engel (1980), identified that the patient's body is the focus of the treatment. The model associates with the passive role of patients as a recipient or follower of doctors' prescriptions (Atkins, 2004, Best et al., 2015). The characteristics of the illness such as the severity of the symptoms and the prognosis as well as treatment complexity, duration, and side effects of the medication regimen are identified as relevant factors to non-adherence (Gadkari and McHorney, 2012, Kardas et al., 2013, Rodriguez et al., 2013). This theory motivated some innovations to promote adherence such as packaging different medications into single pockets and using electronic monitoring devices such as the Medication Event Monitoring Systems (Amico et al., 2013, Munro et al., 2007, Sabaté, 2003). It also provided guidance to develop the physiological measurement of compliance (e.g. detecting drug metabolites in patients' blood sample). However, it is worth considering that high adherence is not always associated with enhanced health outcomes (Berben et al., 2011).

There are some limitations related to the biomedical perspective. The patient's psychological factors, socio-economic environment or demographics as well as the effect of healthcare system and healthcare provider's behaviour are ignored in the description of barriers to non-adherence by this model (Amico et al., 2013, Munro et

al., 2007). In the present study, therefore, it was improbable that the biomedical theory could assist considerably to develop and refine the mHealth intervention to promote cardiovascular medication adherence due to the presumption of the passive role of patients and the major concentration on just the biological illness itself.

2.1.2 Communications Model

Similar to the biomedical approach, the communications model perspective perceives the patient as a trainee who asks for the professional's advice and seeks treatment of the healthcare provider (Manias, 2010). The model emphasises the importance of patient-provider communication. The patient's satisfaction with the practitioner's friendliness, warmth, empathy, interest, and concern associates positively with adherence (Kardas et al., 2013, Sabaté, 2003). Although acceptance of the prescriptions adherence depends on acceptance of the information about the health threat itself, the healthcare provider must also be able to convince the patient that the therapy is beneficial via generating positive attitudes toward health advice (Kardas et al., 2013, Munro et al., 2007). Health advice must not only be well specified in terms of timing, construction, comprehension and clarity of its organisation but also it must be delivered in a way that will enable the patient to attend to and process it thoroughly (Linsky et al., 2015, Murad et al., 2014). The clinician also must have the ability to encourage the patient that the therapeutic regimen is beneficial; it means that he must provoke positive attitudes toward the recommended advice and action plans (Lee et al., 2013). Action plans not only define the accurate actions to be taken such as taking exact dose of a medication at their prescribed time, they also suggest how the action can be integrated into the patient's daily routine (Lally and Gardner, 2013). It is possible by determining the environmental cues as a trigger to remembering to take them at prescribed time and promote its automation (Gardner et al., 2012, Lally and Gardner, 2013).

While receiving, understanding, digesting, and accepting the therapeutic regimen is essential for adherence, it is not enough. The model lacks the description of how health-related information actually affects behaviour change and so leads to the treatment adherence (Gardner et al., 2012). Moreover, the focus of this model is mainly on the patient's beliefs about the factors affecting their health status;

however, the concept of beliefs is not a sufficient determinant of patients' motivation to follow recommended prescribed treatment (Montano and Kasprzyk, 2015). Interventions using communication models as a guide may not be successful as a single strategy in improving adherence to medications because of the failure to account for the influence of the individual's motivation, as well as external factors, such as the availability of social support, accessibility and costs of the treatment that may have an important impact on the sustainability of complex behaviours such as medication adherence over the longer term (Munro et al., 2007). Although the model might provide valuable guidance on the development of the mHealth intervention in this study to improve medication adherence through enhancing patient-provider communication, unfortunately, it provides limited descriptions related to the role of positive reinforcement and factors relating to social support on medication adherence. Moreover, the mHealth intervention was not an educational intervention indicating that the model would not be the most appropriate to be applied in this study.

2.1.3 Rational Belief (Cognitive) Models

The Rational Belief (Cognitive) models propose that individuals are more likely to choose the action that potentially leads to positive outcomes (Munro et al., 2007, Montano and Kasprzyk, 2015). The assumption is that human behaviour is specified by an objective as well as a logical thought process and hence providing the comprehensive information on health risks and the advantages and disadvantages of various behaviours, patients will change their behaviours to maintain their health (Munro et al., 2007). In this way, it can be predicted that inadequate knowledge of the benefits and/or consequences of involving or not involving in prescribed health behaviours are more likely to cause adherence/ non-adherence behaviour (Leventhal and Cameron, 1987, Montano and Kasprzyk, 2015). A short description of each of the relevant models (i.e. Health Belief Model, The Protection Motivation Theory, Social Cognitive Theory, Theory of Planned Behaviour/ Reasoned Action and Information-Motivation-Behavioural skills (IMB) Theory) will be presented next, with a synthesised appraisal of them to conclude.

Health Belief Model

The health belief model developed in the early 1950s to explain precautionary actions, has been developed to be utilised in the study of the compliance in relation to health recommendations and treatment regimens with four basic dimensions indicating the balance between the barriers to and benefits of action (Leventhal and Cameron, 1987, Montano and Kasprzyk, 2015, Munro et al., 2007). The dimensions are: (1) perceived likelihood of a hazard or susceptibility to a specific health condition; (2) perceived seriousness of the hazard including consideration of health and social outcomes; (3) perceived advantages, or the feasibility and effectiveness of the specific health behaviour; and (4) perceived limitations, or difficulties to engaging in the behaviour (Montano and Kasprzyk, 2015). The first two dimensions indicate the person's risk perception as well as motivation for taking action. The third and fourth dimensions imply the cost evaluation of applicable behaviours and identify the specific action to be taken (Montano and Kasprzyk, 2015).

The Protection Motivation Theory

According to the protection motivation theory (1975), behaviour change may be obtained by application of person's fears. The assumption is based on three components of fear stimulation:

- the consequence of threat of a described condition;
- the likelihood of that condition's happening; and
- the effectiveness of the defensive response.

This is the only theory among other cognitive models that explicitly uses the advantages of existing and recommended behaviour to anticipate the probability of change; however, the influence of social, psychological and environmental factors on motivation requires consideration when using this approach (Munro et al., 2007).

Social Cognitive Theory

Bandura's Social Cognitive Theory (1998) postulates a multifaceted causal structure in the organisation of human motivation, action and well-being and includes adherence predictors and guidelines for its promotion based on a continuous, dynamic interaction between the individual, the environment and behaviour (Munro et al., 2007). Social cognitive theory illustrates the importance of

self-influences for change such as beliefs regarding personal efficacy, in addition to knowledge of health risks and benefits as change requirements (Bandura, 2004). Health behaviour is also influenced by the expected outcomes including positive and negative effects of the behaviour or even social approval or disapproval of an action (Munro et al., 2007). Behaviour change may be due to the reduction or elimination of perceived facilitators and barriers (Bandura, 2004, Sheeran et al., 2017). Therefore, this theory describes that behaviours are achieved if people perceive that they have control over the outcome, that there are few external barriers and when individuals have confidence in their ability to execute the behaviour (Armitage and Conner, 2000, Sheeran et al., 2017).

Theory of Planned Behaviour/ Reasoned Action

Based on the theory of reasoned action and planned behaviour assumption (1985), most socially relevant behaviours are under unforced control, and that an individual's intention to take a particular action is the immediate and the best predictor of that behaviour. The individual's intention is impacted by attitudes towards the action, including the individual's beliefs, evaluations of the behaviour outcome, subjective norms or the perceived expectations of important others with regard to a person's behaviour and the motivation for a person to comply with others' wishes (Ajzen, 2011). This theory fails to consider the fact that behaviour may not always be under volitional control; the impacts of past behaviours on current behaviours and more conceptualisation, definition and additional explanatory factors should be taken into consideration (Stroebe, 2000, Sutton, 2010).

Information-Motivation-Behavioural skills (IMB) Theory

This theory includes three components that lead to behaviour change: information, motivation and behaviour skills necessary to perform the behaviour (Fisher and Fisher, 1992). Information refers to the relevant knowledge about a medical condition or prescribed medications, and is a necessary prerequisite for behaviour change but not adequate in isolation (Davis et al., 2015, Fisher and Fisher, 1992). Motivation including both personal and social motivations, is the second component and encompasses individual attitudes towards adherence; the patients' perception of social support from significant others for the behaviour; and perceived subjective norm or perceived others' behaviour with the condition (Sabaté, 2003,

Davis et al., 2015). Behavioural skills results from factors such as ensuring that the patient has the ability to perform the behaviour task as well as a sense of self-efficacy to achieve the behaviour (Davis et al., 2015, Fisher and Fisher, 1992).

It is necessary to take into consideration that all three components of the theory need to be relevant for the desired behaviour to be useful (Fisher et al., 2006, Sabaté, 2003) A range of moderating factors have been identified that have an impact on adherence behaviour such as living situations and access to medical services (Fisher et al., 2006). The presence of both information and motivation are thought to develop behavioural skills, which ultimately result in desired behavioural change and its maintenance (Davis et al., 2015, Fisher and Fisher, 1992, Sabaté, 2003). The main advantage of IMB is its clarity. It is a simple theory that was developed and tested among people received Anti-Retroviral Therapy (ART) in resource-rich settings (Amico et al., 2005). Therefore it may be a promising model for application in the promotion of adherence to long-term medication treatment.

Appraisal of Rational Belief (Cognitive) Models

Specifically, these theories are largely dependent on rational processes focusing only on the norms related to the acceptability of an action. Moreover, the impacts of emotions, social support and even religious beliefs on behaviour and the hazard's threat are ignored (Munro et al., 2007, Montano and Kasprzyk, 2015).

A weakness of the health belief model is that the dimensions are not moderated by each other; they also have an additive effect on health behaviour directly and remain unmediated by behavioural intentions (Munro et al., 2007). Furthermore, determinants of health behaviour, such as the positive effects of risk behaviours and social impact, are not included (Stroebe, 2000).

The Health Belief Model, The Protection Motivation Theory, Social Cognitive Theory, Theory of Planned Behaviour/ Reasoned Action and IMB Theory do not consider coping skills, in particular; they recognise the perceived absence of skills as a 'barrier' or 'cost' (Leventhal and Cameron, 1987, Montano and Kasprzyk, 2015). They focus on perception and logic with an emphasis on conscious and intentional behaviour (Munro et al., 2007). However, some behaviours are based on habits rather than decisions (Gardner et al., 2012). Therefore, the wide range of unintentional

actions that make up so much of individual's behaviours is ignored (Munro et al., 2007). Overall, despite the ability of the Rational Belief Models (RBM) to improve prediction of behaviour compared to Biomedical and Communications Models, it appeared that on the whole the RBM was not sufficient to explain unintentional reasons for medication non-adherence.

2.1.4 Self-Regulation Models

Self-regulation is a broad term that encompasses a variety of processes by which individuals follow and achieve goals. These processes involve both those that are commenced intentionally, as well as those that are more unintentional and initiate unconsciously (Mann et al., 2013). Leventhal's self-regulative models (1984) conceptualise the individual as an active problem solver whose behaviour such as adherence to a health recommendation reflects an attempt to close the perceived gap between their current status and a goal, or ideal state. The model identifies three stages or sets of variables regulating the adaptive behaviour elicited during a health episode. These stages are:

- The cognitive representation of the health threat, which includes several dimensions such as perceived identity of the threat, potential causes, possible consequences, and perceptions of how the health threat shapes itself over time;
- The action plan or coping stage, in which the individual formulates and begins a plan of action; and
- The appraisal stage, in which the individual utilises specific criteria to measure success of one's coping actions, with perceptions of insufficient progress leading to modifications of the representation and/or coping plans (Leventhal and Cameron, 1987).

Different people will construct different mental representations of the same illness threat and may perceive different action plans to be appropriate for the containment of the threat (Munro et al., 2007).

The main limitation of the model is its complexity to use because of its multivariate and transactional character (Leventhal and Cameron, 1987, Mann et al., 2013). Because they are multivariate, the investigator must deal with conceptualising

and measuring multiple factors in a single study, while there is a lack of standardised measurement tools (Mann et al., 2013). The transactional nature forces the researcher to decide when a given variable is to be used as an independent or dependent measure (Lazarus and Folkman, 1984, Mann et al., 2013). In a study by Munro et al. (2007), The sufficiency of the Self-Regulation Models for developing interventions to improve long-term medication adherence was reviewed. From the findings, the authors concluded that although the Self-Regulation Models seem probably appropriate to promote adherence behaviour, it provides inadequate guidance about the interventions design. Therefore, the use of the Self-Regulation Models in the development of mHealth adherence intervention appeared to be inappropriate since it was not clear how these processes could enhance medication adherence.

2.1.5 Behavioural (Social-cognitive) Models

Behavioural models, derived from the learning theories were developed by Pavlov, Skinner, Hull and Tolman (Leventhal and Cameron, 1987). These models describe the effect of the stimuli or cues that elicit behaviour, the rewards that boost the behaviour, the progressive structuring or patterning of the behaviour, and its maintenance after adequate repetition. Bandura (1977) applied concepts from social cognitive theories such as vicarious learning or modelling to add a cognitive ‘thrust’ to the behavioural models (Leventhal and Cameron, 1987). The principles of these models are based on internal (thoughts) or external (environmental) cues while consequences may be negative/ punishments or positive/ rewards for behaviour; The likelihood of a patient continuing a specific behaviour will be partially related to these variables (Munro et al., 2007, Sabaté, 2003).

Behavioural approaches have been applied particularly in attempts to change unhealthy risk habits or lifestyle such as weight reduction, smoking cessation and alcoholism in which the problematic behaviours are changed in response to strong internal or external signals (Davis et al., 2015, Gardner et al., 2012, Leventhal and Cameron, 1987). Strategies pertaining to improving adherence guided by this perspective such as medication reminders have been reported to be effective for adherence to long-term medications (Haynes et al., 2008, Nieuwlaat et al., 2014).

One of the important drawbacks of the behavioural approaches is high rates of relapse after behavioural interventions. It may be due to the discontinuation of reinforcements from the person's environment while cues for the non-adherence behaviours remain (Leventhal and Cameron, 1987, Munro et al., 2007). Another shortfall of the behavioural theories is the failure to account for the underlying psychological mechanisms, conscious and non-conscious, emotional and non-emotional processes in the modification of health behaviours (Davis et al., 2015, Leventhal and Cameron, 1987). The learned approaches must be both automatic and unforced to be effective in improving adherence behaviours even after the programme has been stopped (Davis et al., 2015, Sabaté, 2003). Interventions guided by behavioural theory should follow a multifaceted programme in which reinforcing desired behaviours is associated with social influence, cognitive and motivational factors of behaviour modification (Davis et al., 2015, Leventhal and Cameron, 1987, Munro et al., 2007, Sabaté, 2003).

The intervention of text message medication reminders that was used in this study might be considered as external stimuli to promote patients' adherence behaviour. For the purpose of the present study, Bandura's Social Cognitive Theory provided the framework from which this study approach has been developed. Self-efficacy is a major element of Social Cognitive Theory because it has an impact on patients' motivation and behaviour learning.

In order to clarify the reason to choose Bandura's theory as a guide in this study, it is important to describe that how the mobile phone text-messaging might improve medication taking behaviour. Mobile phone text-messaging interventions can be applied to increase patients' self-efficacy (e.g. sending medication reminders) or establish a form of social support from healthcare professionals. By enhancing self-efficacy and facilitating social support, mHealth interventions may affect health behaviours and increase self-management of CHD and adherence to cardiovascular medications (Bandura, 2012). Text message reminders may have the potential to be useful in this context by providing patients with post-discharge follow-up and by promoting enhanced adherence to medications, or as a channel of patient-provider interaction and support. In addition, medication reminders may enhance CHD patients' self-management, and in this way improve patient self-confidence to

perform the health behaviours essential to achieve a planned goal (i.e. medication adherence behaviour).

The application of self-efficacy enhancing strategies may result in more effective interventions and health promotion programmes. Methods currently employed by healthcare professionals in preventive health care and health promotion programmes and interventions may already use self-efficacy. However, by focusing on the self-efficacy construct, greater success at behaviour change may be obtained.

Following consideration of aforementioned theoretical frameworks, the merits of self-efficacy as a key component of the Social Cognitive Theory and behaviour change interventions were judged to outweigh the merits of other possible approaches presented. This decision also took into account the practical aspect by which an intervention could be administered after hospital discharge during a cardiac rehabilitation programme. It is the use of self-efficacy and the theory from it is derived that was used to shape the investigation of this study and upon which the study mHealth intervention was based.

2.2 Self-efficacy

It is important, at first, to define self-efficacy and understand the mechanisms that impact medication adherence when developing and evaluating effective approaches. Self-efficacy refers to the individuals' beliefs in their own abilities to produce certain attainments that have an impact on a person's life (Bandura, 2012). In a study by Bandura and Locke (2003) exploring how self-efficacy beliefs act in agreement with goals, nine meta-analyses were evaluated. The authors concluded that perceived self-efficacy and individual goals can promote motivation and achievements. They also described that efficacy beliefs influence behavioural functioning as well as behavioural changes over time between people with different perceived self-efficacy level. Self-efficacy has been recognised as the most important predictor for health behavioural change (Bandura, 2012), of which long-term medication adherence in chronic illnesses is an example of one.

Self-efficacy is a major concept and influences level of motivation, affective states, and action (Bandura, 2012). Perceived self-efficacy that is modifiable has been identified as the "cornerstone" of medication adherence (McCann et al., 2008).

Based on empirical findings and theoretical evidence, perceived self-efficacy can have impact on medication adherence in a variety of chronic conditions (Walker et al., 2014, Wu et al., 2015, Schoenthaler et al., 2009). For example, Walker et al. (2014) studied the effect of self-efficacy on diabetic control, medication adherence, self-care, and quality of life. The authors found that higher self-efficacy was related to optimised glycaemic control ($P < 0.001$), medication adherence ($P < 0.001$), self-care ($P < 0.001$) and health related quality of life ($P < 0.017$). Another study undertaken by Wu et al. (2015) examined the relationships between self-efficacy and medication adherence in patients with Heart Failure (HF), it reported that poor medication self-efficacy was linked to low medication adherence ($P < 0.001$). Similar findings were also shown among hypertensive patients ($P < 0.001$) in a study by Schoenthaler et al. (2009). According to a systematic review of 28 studies that provided a systematic examination of the effect of self-efficacy on health outcomes among cardiovascular patients, it was found that higher levels of self-efficacy have an association with improved health outcomes of people with cardiovascular diseases (Gancarczyk et al., 2014).

According to Bandura and McClelland (1977), efficacy expectancies are gained through the four primary sources: performance attainment, vicarious experience, verbal persuasion and physiological state. Perceived self-efficacy has an impact on behavioural aspects, such as the attainment of a new behaviour or the changing of an existing behaviour (Bandura, 1998, Bandura and McClelland, 1977). Bandura (2002) suggested that in order to enhance an individual's sense of self-efficacy, self-regulative skills need to be developed. This requires that people learn how to monitor the behaviour that they wish to change, or how to set realistic goals, and learn how to acquire social support and rewards so that they will be able to maintain the attempt required to succeed.

The development of the mHealth adherence intervention using SMS text-messaging to enhance self-efficacy in medication taking may improve self-efficacy through providing social support (e.g. from nurses or other healthcare providers); or enhance social networks (peer support networks) (De Jongh et al., 2012). These interventions may improve health behaviours and self-management of chronic conditions by enhancing self-efficacy and providing support (Bandura, 2012).

According to the findings of current empirical studies, mHealth interventions aimed at promoting cardiac patients' self-efficacy, significantly enhanced adherence to medications and recommended diet, increased physical activity and ability to stress management (De Jongh et al., 2012, Dale et al., 2015, Park et al., 2014). In the present study, the goal of sending automated SMS prompts was to provide patients with the appropriate self-belief, enhancing self-efficacy, thus enabling them to self-medicate, and retain control of his or her medicines. According to Holloway et al. (2006) who applied theoretical concepts of the self-efficacy construct in developing a behavioural change brief intervention to improve problem drinkers' self-efficacy, reducing alcohol consumption would provide a sense of success. This achievement would in turn increase the likelihood of improvement in the person's perceived self-efficacy level. The authors described that this self-belief could subsequently be developed, and built upon through success and mastery, with their efforts leading to the reduction in alcohol drinking. Similarly in the case here, it was anticipated that improving cardiovascular medication adherence through behavioural change would enhance patients' health outcomes and reduce negative consequences of CHD that would consequently provide a sense of achievement and success; the overall effect of the SMS medication reminders would be a likely improvement in the patients' level of perceived self-efficacy. The sense of success could potentially build up the patient's self-efficacy in medication taking leading to the adoption and maintenance of medication adherence behaviour and ultimately behaviour change. Considering the four principle sources of self-efficacy, verbal persuasion is addressed during the preliminary educational/ informative session of CR programme. Furthermore, prompting of medication using text message reminders was persuading, reinforcing and reminding patients to take their medications. Receiving regular medication reminders in addition to CR educational session would increase patients' awareness that incorporates physiological state. Moreover, medication reminders serve as social support from nurse/ healthcare provider - encouraging patients to take their medications that may incorporate social persuasion. In terms of vicarious experiences, study participants were not restricted from situations that could affect their vicarious experience. During CR sessions, they could talk to other CHD patients who received text-message medication reminder and its effect on their

medication taking. Regarding performance attainment or mastery experience, patients self-monitor their performance and their improvement during CR sessions and those who take their cardiovascular medications regularly can start their scheduled exercises. In other words, they measure success in terms of self-improvement. This could be a positive feedback for this group of patients that persuade them to be more adherent to their medications. Moreover, all participants are routinely assessed at the end of the study and the results are compared to the patients' baseline data. During the follow up session, their improved level of medication adherence together with other clinical outcomes (i.e. their achievements) would indicate performance attainment or mastery experience.

It is important to assess the patients' self-efficacy in medication adherence using a validated and reliable tool, thus, a Medication Adherence Self-Efficacy Scale (MASES) has been developed by Ogedegbe et al. (2003) to measure patients' self-efficacy in taking prescribed medications and determining situations in which people have difficulty in following their medication regimen. The MASES has been used in this study as a research instrument to evaluate the effect of the mHealth intervention to promote patients' self-efficacy in medication adherence (see Section 5.3). In conjunction with the use of self-efficacy, the WHO multi-dimensional model was utilised that is described in Section 2.4. When discussing the importance of applying the most appropriate behaviour change theory to inform interventions, it is necessary to understand the role of specific behaviour change techniques for use within interventions.

2.3 Behaviour Change Techniques

The intervention components influencing behaviour can be mapped on to particular Behaviour Change Techniques (BCTs) to ensure the intervention is evidence-based and guided by an appropriate theory (Michie et al., 2014). While behaviour change interventions have different scope, design and behaviour change techniques, all could benefit from the application of behaviour change science. This science applies theoretical frameworks related to behaviour and behaviour change that are subjected to rigorous and comprehensive evaluation. There are a variety of modals of human behaviour. The issue therefore is which model could be most

appropriate for the delivery of health behaviour change. There is limited evidence available to support the application of any one theoretical framework in particular. For this reason, three routes to behaviour and behaviour change have been identified in the Health Behaviour Change Competency Framework (HBCC) by Dixon and Johnston (2010): Motivation development to promote skills that help that motivation to be transformed into Action; and Prompted or cued routes to behaviour (MAP). The route MAP is a valuable model to summarise the main principles of various behaviour change theories. Research continues to target one of the MAP routes to change by the BCTs delivered across different settings and behaviours including medication adherence (Bobrow et al., 2016, Dusseldorp et al., 2014, Kamal et al., 2015). However, according to the emerging literature focusing on MAP-based interventions, there has been criticism that there is not a complete understanding of the useful and crucial components of behaviour change interventions (Dixon and Johnston, 2010, Kok et al., 2016). A meta-analysis of the influence of using theory on the effectiveness of health behaviour interventions showed that generally there is a weak relationship between the extent of theory use and the type of the applied theory with the intervention effectiveness (Prestwich et al., 2014). Another issue, according to Hardcastle (2016), is that the current BCT taxonomies do not elucidate the importance of client-provider relationship that could be incorporated into the intervention content to improve the intervention effectiveness. Together, these critiques highlight that some behaviour change interventions have not been informed by the available evidence and that further research is needed in order to formulate the most beneficial techniques for improving medication adherence. In this study, the mHealth medication adherence intervention targeted the third route of MAP (i.e. the prompted or cued route) that supports behaviour (i.e. medication adherence) without the need for the constant cognitive attempt required by the other routes (Dixon and Johnston, 2010). The intervention also benefited from the application of the principles of the WHO Adherence Model (2003) in which both intra- and interpersonal factors (e.g. patient-provider communication) have been identified as important dimensions to increase adherence alongside the Bandura's self-efficacy theory.

2.4 The WHO Multi-dimensional Adherence Model

While the focus of the behavioural change theories is mainly on factors influencing patients, it has been identified by the WHO Adherence Model (2003) that medication non-adherence is a complex and multi-dimensional issue. Application of the theories focusing on patients and providers can help to develop theory-based interventions focusing on intra- or interpersonal factors to increase adherence; however, it is not the only area in which adherence can be promoted (De Jongh et al., 2012).

Ecological or multilevel system models not only focus on patient behaviour but also on barriers related to environment (Kidd and Altman, 2000). Ecological models include intrapersonal, interpersonal, bureaucratic, policy-making, and community obstacles such as patient-provider communications, access to health care, medication availability, social support, and complexity of medication regimen (Glanz et al., 2008). The WHO Multidimensional Adherence Model (2003) is an example of ecological models that complements the elements of self-efficacy and was therefore also adopted to be used in this study.

In 2003, the WHO described adherence to long-term therapies as a behaviour that is influenced by multiple barriers. The model encompasses interactions between five sets of factors termed "dimensions" that ultimately affects patient outcomes. These dimensions are:

- A. Social and economic factors,
- B. Therapy-related factors,
- C. Condition-related factors,
- D. Healthcare team- and system-related factors and
- E. Patient-related factors.

Each dimension is briefly described in Table 2.1.

Table 2.1. Description of the WHO Multi-dimensional Adherence Model (2003)

Socioeconomic factors	The main socioeconomic concerns with a great effect on adherence are: poverty, difficult accessibility to medical centers and medications, illiteracy, lack of social support, thoughts and beliefs about diseases and treatments that could affect health service delivery.
Therapy-related factors	Among therapy-related factors, dose frequency, complicated medication regimen and the medications' side-effects were identified as important barriers to adherence.
Condition-related factors	Condition-related factors represent specific disease-related needs experienced by the patient such as symptoms intensity, level of inability, disease intensity and progression, and availability of the efficient treatment.
Healthcare team-/ system-related factors	Among system-related factors, the way that healthcare systems operate, accessible services and resources types, and the way in which healthcare providers deliver treatments are of the most important concerns. It was also described in the model that there are five main barriers related to healthcare system-related factors including lack of awareness and information about adherence; lack of approaches to assist patients in modifying maladaptive healthy behaviors and learn adaptive ones; lack of efficient interaction between patients and healthcare providers
Patient-related factors	Major concerns related to the patient-related factors are forgetfulness, carelessness, anxiety about the complexity of medication regimen, lack of motivation, and misunderstanding of treatment instructions.

The WHO Multi-dimensional Adherence Model was relevant to remodel and evaluate the intervention used in this study as it emphasises on the presumption of the active role of patients in their treatment and considering multiple factors related to long-term medication adherence. According to the model, it could not be possible for only one determinant to be responsible for medication non-adherence. Therefore, appropriate interventions should address multiple barriers to adherence. In this way, a nurse-led mHealth medication reminder intervention may have the potential to improve cardiovascular medication adherence through addressing most common barriers to adherence such as patient-related factors (forgetfulness, carelessness and low self-efficacy in taking medications) and healthcare system-related factors (patient-provider interaction and social support) during the early phase of hospital post-discharge in parallel with outpatient CR programmes.

2.5 Summary

The component of health behaviour change is formed by the Social Cognitive Theory (SCT) (Bandura, 2004). Self-efficacy, a major construct of SCT and a mediator of behaviour change, is the individual's confidence to operate a desired behaviour (Bandura, 2012). The progress of adoption and integration of medication

taking into the individual's daily routine can be facilitated by the use of technology to improve behavioural approaches such as self-care management and positive reinforcement (Bosworth et al., 2011). mHealth interventions using text message reminders as a type of social support from healthcare providers to improve medication adherence, (such as the one used in this study), are primarily based on the principles of self-efficacy within the SCT, one of the five theoretical perspectives related to medication adherence outlined by Leventhal and Cameron (1987). It was proposed in this study that receiving SMS text messages about medication reminders in addition to educational information about self-care of CHD (provided in the first session of hospital-based CR) would enhance patients' self-efficacy to take cardio-protective medications as prescribed.

According to the WHO Multidimensional Adherence Model (2003), there is no single determinant that influences medication adherence to treatment and so the issue of non-adherence is complex and multidimensional. Interventions aimed at improving adherence need to be adjusted to address the patients' reasoning for non-adherence to medications (Bosworth et al., 2011, Brown et al., 2016, Costa et al., 2015). The intervention for this research study was also guided by the WHO Adherence Model to improve cardiovascular medication adherence in CHD patients by focusing on the leading causes of medication non-adherence that are unintentional on the patient's part (forgetting, carelessness and poor self-efficacy), as well as system-related factors (patient-provider interaction and support after discharge).

CHAPTER 3: LITERATURE REVIEW

This chapter includes ten sections in which the literature pertinent to the undertaken study is reviewed, critiqued and synthesised. The aim of the review is to identify gaps in the current evidence base and develop a research question through critiquing literature pertaining to mHealth interventions that have been developed and/or implemented to address medication adherence in CVD. This Chapter begins with a description of the search strategy followed by a review of the literature examining mHealth interventions used to improve medication adherence in chronic conditions with a specific focus on using mobile phone-based medication reminders for CVD patients.

In order to develop an effective search strategy (see Table 3.1), the PICO - the Patient, Intervention, Comparison and Outcome – criteria/model was used to assist in the framing of a “foreground” research question (Sackett et al 1997). From the foreground question, separation of the question parts meant the subject area was more easy to search (Aslam and Emmanuel, 2010). Once the literature was retrieved, a researchable question was identified.

Table 3.1. Search Strategy

Group	Adults
Age	Over 18
Gender	Male and/ or female
Year	January 2003 to June 2017
Research Methods	Randomised Controlled Trial, Trial, Pilot, Feasibility, Evaluation, Process Evaluation, Literature Reviews, Systematic Reviews, Meta-analysis, Surveys, Qualitative and Focus Groups
Language	English Full text, English Abstract

After establishing useful text words and MeSH headings with relevant keywords, all possible synonyms and alternative spellings for the specific concepts or terms were considered to increase the sensitivity of the search and not miss important information (see Table 3.2). Then Boolean Operators were used to combine them. Truncation or wildcards was used based on the database's help pages to retrieve all possible variations and increase the flexibility and efficiency of the search. When appropriate, the "adjacency searching" applied to find search terms

appear near each other in a sentence. A list of used keywords can be found in Table 3.2.

Before searching the literature, inclusion and exclusion criteria were formulated. Publications written in English were included, as the researcher could read and understand the language. The time span of the literature search was limited to January 2003 to June 2017 for studies that evaluated medication adherence in response to mHealth interventions in patients with cardiovascular disease. An email alarm was set to receive updates and accepted papers ahead of print. The reason for applying a year limit in the search process was to obtain recent and updated information about the issue. Moreover, the WHO published a document for the first time in 2003 in which medication adherence was defined as a medical and public concern that need to be addressed with respect to all chronic conditions regardless of their cause. Based on the study focus, the following were set as the inclusion criteria:

- Review or trial mHealth as the main study focus;
- Study utilised mHealth by adults (>18 years) of both gender;
- Be in English language;
- Be published between January 2003 and June 2017.

Duplicates were removed and articles were excluded if they exhibited one or more of the following characteristics:

- The patient was not the study target population (i.e., provider-focused);
- Described a study protocol;
- Involved children and/or people younger than 18 as the target population;
- Used mHealth for acute conditions;
- Used mHealth for assessment, monitoring or measurement;
- Proposed or developed a model or device.

There were no restrictions with regard to patients' sex, and ethnicity and study location.

Table 3.2. List of used keywords and search results

NO	SUBJECT HEADING	KEYWORDS	RESULTS
1	Cardiovascular diseases/ or heart diseases/ or myocardial ischemia/ or acute coronary syndrome/ or coronary disease/ or angina pectoris/ or myocardial infarction	heart or cardi* or coronary or CHD or CVD or CAD or "myocardial infarction*" or "myocardial ischemia*" or angina or "cardiovascular disorder"	Global Health, PsycINFO, Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE: 5,569,280 Cochrane: 192,778 CINHAL: 377,146 Web of Science for Conference Papers: 5,449
2	Telehealth/ or text messaging/ or reminder systems/ or Telephone or Mobile Applications	telephone* or phone* or smartphone* or "text messag*" or "mhealth" or SMS or "text reminder*" or "medication reminder*" or "automatic reminder*" or "mobile health" or "telemedicine" or "telehealth"	Global Health, PsycINFO, Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE: 357,550 Cochrane: 19,618 CINHAL: 57,026 Web of Science for Conference Papers: 5,854
3	Patient Compliance/ or Medication Adherence	(Medic* or drug\$ or pill\$ or prescri* or treatment\$ or pharma* or "medic* taking") AND ("non adherence" or nonadherence or "non compliance" or noncompliance) OR (compliance or adherence)	Global Health, PsycINFO, Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE: 467,137 Cochrane: 37,347 CINHAL: 60,289 Web of Science for Conference Papers: 937
4	1 AND 2 AND 3	Total: 4599 , Remove duplicates: 3120, Apply year limit: 2934 Irrelevant: 2368, Not in English: 54, <18 years old patients: 239, Patient is not target population: 25, Protocol study:42, mHealth used for assessment, monitoring or outcome measurement:118, Proposed a model or develop a device/ program: 9, No mHealth approach: 13, Not an Empirical Research: 53 Full-text articles assessed for eligibility:13	

The abstracts of the publications resulting from all search strategies were screened for relevancy. If the abstract did not provide sufficient information, then the full text was scanned to determine whether or not the publication met the inclusion criteria. The quality of relevant studies was analysed based on critical appraisal tools such as CONSORT – CONSolidated Standards Of Reporting Trials (Appendix 1).

3.1 Data Extraction and Analysis

The Search Strategy used in this review were assessed by a librarian (RS) and two other reviewers (AH, CCh) and corrections were made when necessary. Publications were initially screened for potential inclusion based on the review of title and abstract by the main researcher (SKh). Inclusion of selected trials were finalised separately and then together by consensus among SKh and the second reviewer (AH). Information including objectives, types of mHealth intervention used, setting, study sample characteristics, outcomes measured, and results reported were extracted using Microsoft Excel. Studies were organised for analysis based on the study target population (i.e. Chronic Cardiac and Non-cardiac Conditions). Usability, feasibility, and acceptability of the mHealth intervention used among study groups, the effect on patient adherence to chronic medications, and disease-specific clinical outcomes of the intervention were reviewed. A descriptive review of the studies was performed and the findings from these research studies summarised, with emphasis on results reported in trials. Differences between study groups were highlighted when these results were available.

3.2 Search Results

The electronic databases CINAHL (Cumulative Index of Nursing and Allied Health Literature), Cochrane, Campbell Collaboration, Medline, Embase, GlobalHealth and PsycINFO were searched and 4599 records were found using the keywords/ subject terms noted in Table 3.2. Additional articles were extracted using Grey literature databases including OpenGray, GrayLIT Network, MAGiC (Managing Access to Grey Literature Collections), ProQuest Theses Global, Web of Science for Conference Papers. Government Documents and websites of relevant organisations including Charities, Health Institutes as well as International agencies such as the World Health Organisation (WHO) were searched as well. 4 articles were included through searching grey literature, table of contents and journal indexes and the lists of references of relevant articles. 2934 records were included after duplicates removed and year limit applied. Then, the title and abstracts were reviewed and 2368 irrelevant studies were removed. Finally, out of 566 remaining records 553 were excluded and identified 13 trials matching selected inclusion criteria (Figure 3.1). For simplification purposes, trials were classified and tabulated according to the year of

publication (see Appendix 2). Table 3.3 presents a checklist of reporting criteria as recommended by CONSORT.

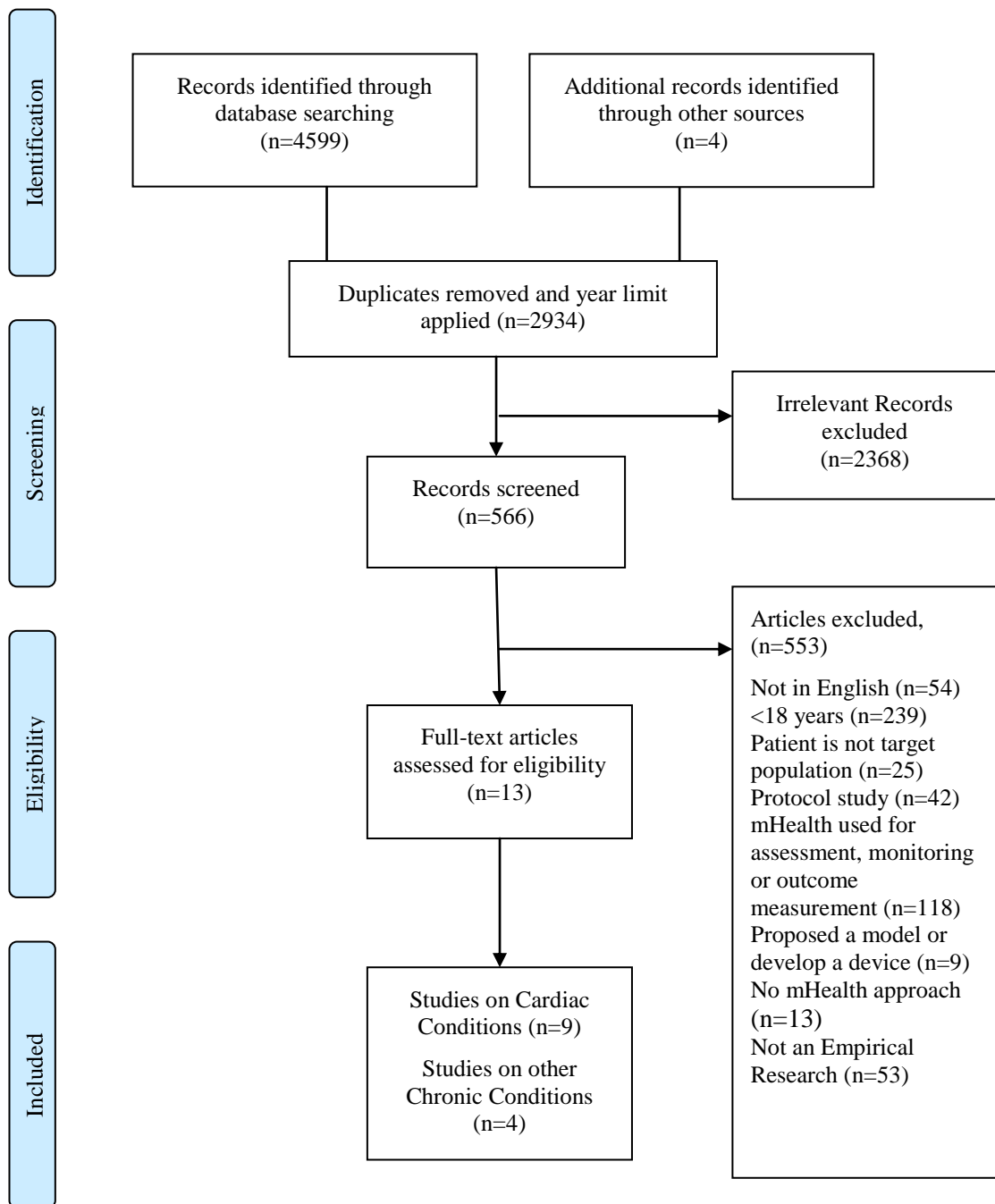


Figure 3.1. Flow chart of the literature review search

Table 3.3. Quality assessment using CONSORT guidelines for Randomised Controlled Trials

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total	
Strandbygaard (2010)	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓		✓	✓				✓	✓					15	
Zolfaghari (2012)	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓				✓		✓				✓	17
Quilici (2013)	✓	✓			✓	✓	✓						✓	✓	✓	✓						✓					11
Arora (2014)	✓	✓	✓	✓	✓	✓	✓					✓	✓	✓	✓	✓				✓	✓	✓	✓				17
Park (2014)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓				✓	✓	✓	✓				20
Vollmer (2014)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓			✓	✓	✓	✓			✓		21
Wald (2014)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓			23
Dale (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓			23
Kamal (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓				✓	✓	✓	✓	✓			22
Pandey (2015)	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓				✓		✓					17
Akhu-Zaheya (2016)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓				✓		✓					18
Bobrow (2016)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓		23
Fang (2016)	✓	✓	✓	✓	✓	✓	✓					✓	✓		✓	✓				✓		✓					13

The CONSORT criteria include: (1) Title/abstract. Introduction: (2) background and objectives. Methods: (3) trial design, (4) participants, (5) interventions, (6) outcomes, (7) sample size, (8) sequence generation, (9) allocation concealment, (10) implementation, (11) blinding, (12) statistical methods. Results: (13) participant flow, (14) recruitment, (15) baseline data, (16) numbers analyzed, (17) outcomes and estimation, (18) ancillary analyses, (19) harms. Discussion: (20) limitations, (21) generalisability, (22) interpretation. Other information: (23) registration, (24) protocol, (25) funding

3.3 Structure of the Literature Review

The remainder of this Chapter has described the characteristic of the selected studies for review in terms of publication years, study setting, target population, duration of trials, sample size and outcome measures. Then, type of mHealth interventions used to address medication non-adherence in a variety of settings, conditions, and populations is reviewed. Selected trials were categorised and discussed based on different types of using mHealth in supporting Medication Adherence (MA) of patients to chronic cardiac and non-cardiac disease management. After that the feasibility and acceptability of mHealth tools and the limitations of trials were reviewed. Theory-based mHealth interventions and the most popular theories used in the studies were discussed, as well. In the final sections, the discussion and conclusion provides a summary from what has been discussed within all Sections in the Literature Review Chapter to highlight the gap in the knowledge and the rationale for the study undertaken.

3.4 Study Characteristics

Publication years ranged from 2010 to 2016, with an overall increase in articles published more recently (Figure 3.2). None of the studies published before 2010 met the inclusion criteria. A total of 23.07% (3/13) of studies were conducted in the United States (US) (Arora et al., 2014, Park et al., 2014, Vollmer et al., 2014). There was one study from each of the following countries: Canada (Pandey, 2015), China (Fang and Li, 2016), Denmark (Strandbygaard et al., 2010), France (Quilici et al., 2013), Iran (Zolfaghari et al., 2012), Jordan (Akhu-Zaheya and Wa'ed, 2016), New Zealand (Dale et al., 2015), Pakistan (Kamal et al., 2015), South Africa (Bobrow et al., 2016) , and United Kingdom (UK) (Wald et al., 2014).

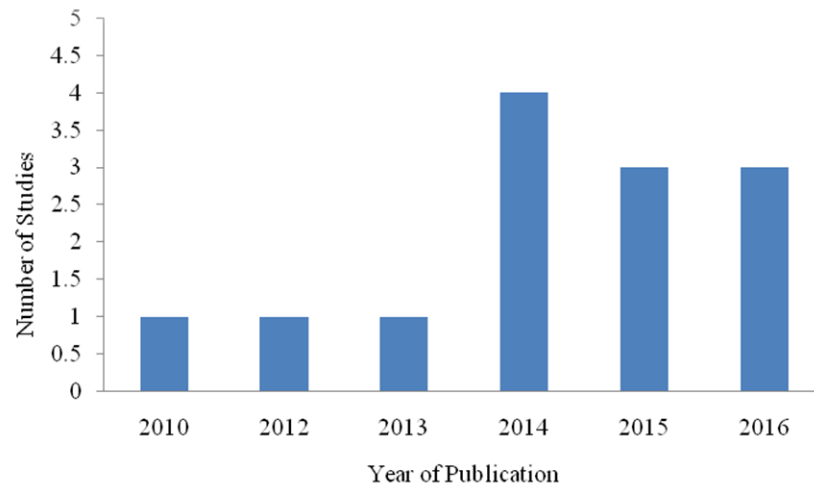


Figure 3.2. Studies published over time

In these studies, 61.5 % (8/13) targeted CVD patients. Other studies evaluated various chronic diseases, including asthma (Strandbygaard et al., 2010), diabetes (Arora et al., 2014, Zolfaghari et al., 2012) hypertension (Bobrow et al., 2016), and stroke (Kamal et al., 2015). Duration of trials ranged from 1 to 12 months. Sample size ranged from 26 to 21,752 individuals. Four studies had a sample size of less than 100. The most popular method of research subjects' recruitment was non-probability convenience sampling. Individuals who have been recruited by convenience sampling were mostly hospital in-patients or out-patient and primary care practice patients.

Less than one third of the studies were nurse-led (Akhu-Zaheya and Wa'ed, 2016, Fang and Li, 2016, Park et al., 2014, Zolfaghari et al., 2012) and Medical Doctors (MDs) were main investigators of the majority of the mHealth studies.

With regards to outcome measures, around 77% (10/13) of the included trials examined medication adherence as the primary outcome. The majority of the studies measured medication adherence using the self-reported Morisky Medication Adherence Scale (MMAS) (Morisky et al., 1986). One study (Park et al., 2014) assessed medication adherence by Medication Event Monitoring System (MEMS) in addition to MMAS. MEMS is an electronic monitoring device that indirectly records date and time of removing a dose of a medication (El Alili et al., 2016). Bobrow et al. (2016) calculated adherence score, using the Proportion of Days of medication Covered (PDC), recorded in the clinical or pharmacy records. The PDC calculation is

based on the fill dates and days' supply for each fill of a prescription (Choudhry et al., 2009). A modified version of PDC (mPDC) was used in a study by Vollmer et al. (2014) including the whole follow-up period as the denominator time frame rather than time from first dispensing. Objective measurement of medication taking was reported in only three studies (Arora et al., 2014, Zolfaghari et al., 2012, Quilici et al., 2013). Quilici et al. (2013) measured patients' adherence to aspirin using Arachidonic Acid-induced platelet Aggregation (AA-Ag) testing after intervention. Arora et al. (2014) and Zolfaghari et al. (2012) measured changes in Glycosylated haemoglobin (Hb A1C) level over the study time in addition to the self-reported questionnaire related to diabetes medications adherence. Strandbygaard et al. (2010) assessed adherence to asthma treatment using medicine count on the inhaler device and pharmacy reports.

The control arm in 10 studies was standard therapy. Fang and Li (2016) compared the text message intervention with a control arm using an additional monthly telephone call to remind them of their medication schedule and upcoming appointments. In the study undertaken by Pandey (2015) there were two intervention arms receiving the same text message reminders but in two different time frames to mitigate a potential trainer effect while there was no control group. Zolfaghari et al. (2012) compared two different interventions (i.e. telephone follow-up with Short Message Service (SMS) on type 2 diabetes adherence with no control arm.

In terms of using a conceptual framework to develop the intervention, less than one third (4/13) of the studies (Arora et al., 2014, Dale et al., 2015, Kamal et al., 2015, Park et al., 2014) were theory-based. The Health Belief Model, Bandura's Self-Efficacy Theory, and Social Cognitive Theory were the most common theories or models used.

3.5 Types of mHealth Adherence Interventions

There was considerable variation in the mHealth adherence intervention characteristics. For the purposes of this review, mHealth-based interventions are classified into four main categories including passive TM reminder; interactive TM reminder; mHealth interventions other than TM reminder; and comparison between two mHealth interventions (Figure 3.3).

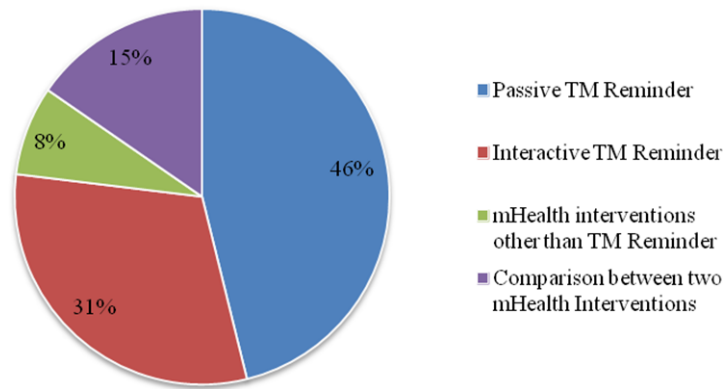


Figure 3.3. Types of mHealth adherence interventions

3.5.1 Passive TM Reminders

Near half of the trials passively sent regular reminders to patients' mobile phones to improve medication adherence. In Denmark, Strandbygaard et al. (2010) sent passive daily TM to participants' mobile phones for 12 weeks to remind them of taking their anti-asthmatic medication. Although asthma is a non-cardiac chronic condition, this study has been selected in this review because the type of the mHealth intervention is of particular relevance to this thesis.

A total of 26 patients aged 18-45 years, with a clinical history of asthma and a positive Methacholine Challenge Test (as they were described by the authors) were recruited via advertisements in free local newspapers and randomised to receive, or to not receive the TM medication reminders. Reminders, at a fixed predetermined frequency, were delivered to the TM group with the following content:

‘Remember to take your asthma medication morning and evening. From the Respiratory Unit’.

The absolute difference in mean adherence rate (the primary outcome of the study) between the two randomisation groups after 12 weeks was 17.8% with 95% Confidence Interval (CI) of 3.2-32.3, $P=0.019$. There were no significant differences between the two study groups for the secondary outcomes including reimbursement of asthma medication, and changes in exhaled nitric oxide levels, lung function measurement, and airway responsiveness to inhaled methacholine. The study authors described that a daily TM reminder has the potential to create a higher awareness of

asthma control and treatment and by implementing this awareness in a patient's daily routine the adherent behaviour is improved. A daily TM reminder, in this Danish study, showed rather larger effect on medication adherence compared to the clinical outcomes. The percentage of the medication taken by the participants measured using a medication usage recorder, the discos Seretide device. The validity of this method of measurement is highly dependent on patients' credibility as they could remove unused medications from their devices before the follow-up visits. Hence, reported results may indicate that there are still ambiguities relating to the effect of TM medication reminders on adherence and clinical outcomes and reliable stable measure or triangulations between subjective and objective measures may probably have shown differences even after a short period of using a mHealth intervention. This study conducted with a small sample size and short-term follow-up indicating that the findings may not be generalisable to a similar chronic condition. All these considerations were taken into account prior to the implementation of the present PhD research when formulating the study objectives and selecting outcome measures.

Similarly, Quilici et al. (2013) used personalised unidirectional SMS reminders for one month with different formulation every day for aspirin intake in Acute Coronary Syndromes (ACS) patients who underwent percutaneous coronary stenting. Five hundred and twenty two patients of those who were admitted to an Antiplatelet Monitoring Unit in France, 30 days after hospital discharge, randomised to receive or to not receive SMS medication reminders. It was shown that daily computer-generated motivational reminders were likely to significantly improve self-reported aspirin adherence, Odds Ratio (OR) [95%CI]: 0.37 [0.15–0.90]; $P=0.02$ and platelet function testing, OR [95%CI]: 0.43 [0.22–0.86]; $P=0.01$, at one month compared to standard care alone. The authors described that transition to home with experiencing post-discharge anxiety and depression may impact on patients' medication adherence and so such inexpensive, widely available SMS-based intervention may offer the potential to improve adherence behaviour and health outcomes. There was no example of text-message content used in this study and explanation of the system development or SMS formulations. Moreover, the study took place with a short follow-up period of only one month that did not provide long-term adherence

behaviour changes or clinical outcomes. According to Lally et al. (2010), an average time needed to reach the automaticity of a desired behaviour is 66 days. In the present PhD study, 12 weeks were considered to evaluate the effect of the mHealth intervention on medication taking behaviour in CHD patients; all stages of intervention development and piloting work were formulated and described based on the Medical Research Council (MRC) guidance for evaluating complex interventions (2015) (see Methods Chapter).

In another study by Arora et al. (2014), a one-way TM intervention called “TEXT-MED” system was developed that sent TM as a trigger for diabetic patients in Los Angeles County to engage in self-care activities and medication adherence. In this study, 153 diabetic patients, aged 18 years or older were identified using the Emergency Department Information System of whom 128 were randomised in either intervention (n=64) or control group (n=64). The TExT-MED sent daily messages (available in both English and Spanish) with maximum 160 characters to participants’ mobile phones twice a day at specific times for 6 months. Message contents were developed based on an iterative process using current National Educational Materials, multidisciplinary expert advice, previous mHealth experience and work with target population for their specific interests. They developed four categories of messages including Educational/motivational, Medication reminders, Healthy living challenges and Trivia (Questions & Answers) that were sent to the patients at a different frequency. For example, medication reminders were planned to be delivered to patients 3 times per week to increase adherence with prescribed medications with following sample:

“Medication reminder! Don’t leave home without your medications”.

It seems that such variety in the developed TM types can be problematic in investigating which message components were most effective and engaging while they reported on the overall programme. Although TExT-MED did not show a statistically significant difference in the primary outcome of Hb A1C, investigators supported their intervention and described that the system requires minimum investment, making them especially appealing to under-resourced organisations. They believed that in terms of familiarity, availability and cost-effectiveness, TM-

based interventions can be brought to a community scale rapidly in comparison with Smartphones. Although the target population of this study is not cardiac patients, the type of the mHealth intervention, its development and TM reminders' contents are of particular relevance to this thesis.

In a three-phase study conducted by Pandey (2015), a computer-based TM reminder system developed as a potential solution to improve adherence to medications in Canadian patients with Coronary Artery Disease (CAD). The researcher described the three phases of their study;

Phase 1: testing the technical reliability and feasibility of the TM reminder system in 4 volunteers with different phones and service providers over a two-month period;

Phase 2: pilot testing in 25 healthy participants divided into two groups to receive TM reminders in four predetermined times per day in either week one or week two; and

Phase 3: evaluating the intervention in 30 cardiac patients equally divided into two groups to receive TM reminders according to their medication regimen in either month one or month two.

It was described that the system was designed to address forgetfulness and unintentional causes of non-adherence. Nevertheless, it showed a significant effect on improving adherence, with all of stable cardiac patients demonstrating reduction in non-adherence with an average relative risk of 64% in this group of patients ($P < 0.01$). The researcher asked participants to record their medication taking in specially designed and supplied logbooks as the only instrument for outcome measurement. This method of measurement may overestimate patients' adherence since the majority of patients do not tend to report undesired behaviour of medication non-adherence in order to make their care providers pleased. There was no example of text-message content or explanation of factors considered in formulation of TM reminders. The small sample size and short-term follow-up may have impaired the validity and generalisability of the study findings.

A more recent study conducted by Akhu-Zaheya and Wa'ed, (2016) in the North of Jordan aimed to evaluate the effect of SMS reminders on adherence to medication, diet and smoking cessation among adult cardiovascular patients.

Hundred and eighty participants were recruited by a nurse from outpatient clinics and randomly assigned to experimental, placebo, and control groups by shuffling numbers allocated to each patients (n=60 per group). Participants in the intervention group received three types of SMS reminders about medications, healthy diet and quitting smoking with the following template, as an example, for a medication reminder message:

“Mr. /Ms. (patient name), please it is the time to take (medication name), (dose) (number of tablet) at (time)”.

There was no information regarding the timing and frequency of SMS reminders. Participants in the placebo group received health-related general messages in their mobile phone. The Control group did not receive any types of intervention.

Participants' adherence to medication, healthy diet, and smoking cessation were assessed by Morisky self-report questionnaire (MMAS), Mediterranean Diet Adherence Screener (MEDAS), and Readiness to Quit Ladder, respectively at the start-point and after 3 months of the study. According to the study findings, there were significant differences between study groups in medication adherence (P=0.001) and adherence to diet (P<0.0001); however, no significant difference was observed between the three groups, in terms of readiness to smoking cessation (P=0.327), and/ or amount of smoking (P=0.34). Using self-report measure as the single approach to assess adherence may lead to the self-reporting bias that alter the validity of study findings.

As it was described by the authors, in developing countries, there are limited post-discharge follow-up at home and so SMS may have the potential to be an accessible way to improve cardiovascular patients' discharge follow-up. However, further research is needed to support the effectiveness of SMS with a rigorous design and accurate outcome measurement.

Fang et al. (2016) used text messaging along with Micro Letter (ML), an online platform messenger service accessible for participants through the Internet Portal via scanning a code or searching the platform name. A total of 280 CAD outpatients from Chengdu City, China, were randomised to three groups: SMS only (n=95), SMS plus ML (n=92), and phone (control) (n=93).

CAD-related information and medication reminders were sent to participants at intervals regularly under a nurse and doctor supervision. This information was delivered to patients in the form of text messages, images, and media content related to the disease. Investigators assessed medication adherence using Morisky self-report questionnaire as the only method of outcome measurement that the results are highly dependent on patients' honesty and may artificially inflated the level of adherence. Both intervention groups showed better Statins adherence after six months than the control group who received one telephone call per month to remind them of their medication schedule and appointments, SMS only vs. Control OR [95%CI]: 0.069 [0.032–0.151]; $P < 0.001$ and SMS + ML vs. Control OR [95%CI]: 0.339 [0.183–0.629]; $P = 0.001$.

The authors discussed that the study intervention provided an easy-to-use, self-service learning platform that participants were able to access the information frequently at their preferred convenience time. However, it needs to be taken into consideration that such intervention approaches may limit rural participants because they are required to have access to cellular networks for SMS and ML information. They also have to be educated and competent with computer and the Internet. Moreover, providing accurate and timely health-related information through SMS and ML requires adequate time, resources and staff training.

In the studies using TM medication reminders as a form of mHealth intervention, it was shown that mobile phone text-messaging have the potential to be widely available, easy-to-use and inexpensive. It is a rapid, convenient communication method and allows sending medication reminders as well as dissemination of disease-related information in a user friendly format with less effort on the part of health care staff or personnel (Thakkar et al., 2015, Gandapur et al., 2016). Overall, the findings of the studies using unidirectional TM reminders have

been mixed. Most of the trials were conducted in a short duration with a small sample size. It indicates that reported findings may not necessarily be generalisable to cardiac medications and so uncertainty remains about the effect of text message reminders to improve medication adherence in cardiovascular patients. Moreover, review of these papers suggested that TM reminder as a mHealth intervention has been evaluated on a small-scale, mainly in developed countries and has done little to add to the existing body of knowledge. Further research is needed to evaluate the effect of mHealth intervention on medication adherence in developing countries.

3.5.2 Interactive TM Reminders

In these studies, 31% (4/13) used interactive TM medication reminders. Park et al. (2014) used personalised interactive TM reminders twice a day to take antiplatelet and statin medications and/or one-way health education three times a week in patients with Coronary Heart Disease (CHD) in Northern California for 30 days.

A convenience sample of 90 patients with CHD who were introduced by other cardiologists or nurses were recruited and randomised to one of three study groups by generating random allocation sequence using blocks of 6. Study groups comprised of 30 participants who received TM Reminders plus TM Health Education; 30 participants who received TM Health Education Alone; or 30 participants who did not receive TM.

Personalised TM reminders were sent at patients' preferred times based on their medication schedule. There was a difference in the number of delivered messages in the two intervention groups. 74 messages over the time of the study were delivered to the TM Reminders plus TM Education group, while 14 messages were sent to the TM Education only group. Patients were required to reply back to confirm the delivery of the TM reminder. Here is an example of reminder content:

“John, take Plavix 75 mg at 9:00 AM. Respond with 1.”

The primary outcome of the medication adherence using electronic monitoring devices, Medication Event Monitoring System (MEMS), revealed patients who received TM for antiplatelets had a higher percentage of correct doses taken ($P=0.02$), percentage number of doses taken ($P=0.01$), and percentage of prescribed doses taken on schedule ($P=0.01$). Nonetheless, Morisky self-reported adherence

revealed no significant differences between groups. Study findings showed better adherence to antiplatelet medications (but not to Statins) in the two experimental groups who received TM for medications compared to those who did not. The authors described that this result was consistent with the poor adherence generally seen with Statin medications. The similar finding was reported that there was a significant lower participants' response to Statins reminders compared to antiplatelet medications. Investigators discussed challenges of obtaining complete MEMS data. Patients did not use MEMS properly due to experiencing higher levels of stress with using MEMS in addition to the anxiety relating to a new diagnosis of CHD and hospital discharge (as they were described by the authors). Some patients tended to use a pill box or were not comfortable in carrying the MEMS device with them while they were away from home. Moreover, MEMS and TM patients' responses may not have indicated the actual medication consumption as patients could have replied to the TM and opened the MEMS without actually taking the medicine. The Hawthorne effect is another limitation of using MEMS or other electronic medication monitoring devices (as they were discussed by the authors). It means that using such devices may have attracted attention to regular medication intake behaviour unintentionally for all groups including the control group. The relatively small sample size and short-term follow-up may have weakened the study power and external validity of the findings, as well.

A similar study carried out by Wald et al. (2014) in London involved an automated computer program to send two-way text messages to CVD patients receiving Blood Pressure (BP) and lipid-lowering medications daily for 2 weeks, alternate days for 2 weeks and weekly for another 22 weeks over the six months period of the study.

Three hundred and three patients were recruited from eligible people who were identified from electronic lists of patients. Investigators sent an invitation TM to 6884 patients asking them to respond back if they were interested in participating in the trial. Another 120 patients were identified when attending their primary health care practice. Participants were randomly assigned in blocks of 4 to receive (n=151) or to not receive TMs (n=152). This method of recruitment might lead to enrolling more attentive patients that were likely to be adherent to their medication in

comparison with other patients in general. Moreover, this may limit the power of the study to show statistically significant results in improving medication adherence.

It was mandatory for participants to response back to each TM reminder, reporting whether they had/ had not taken their drug, or whether they are reminded to take it by TM if they had forgotten. Patients' text reply was filed by the developed computer program automatically. Participants, who had not taken their medications or not replied, received a phone call to identify whether they had a reason for it, and if so, to discuss and resolve the issue. The TMs were tailored to the time that participants consumed their medication but the TM frequency was not automatically modified based on the patients' response.

The finding of this study that examined a two-way TM reminder increased adherence to the use of BP and/or lipid-lowering medication significantly in the intervention group compared to the control, 16% with 95% CI (7%–24%), $P < 0.001$. Medication adherence, in this study, was determined by querying patients regarding any medication discontinuation or missed doses at primary care practice visits or using electronic prescription records of the General Practice (GP). Although self-report adherence measure is low cost and easy-to-use, there are concerns about the validity of these measures. That is because self-report measures are vulnerable to social desirability, question phrasing and recall biases that may overestimate the degree to which patients take medications in comparison to other methods (Stirratt et al., 2015). However, acceptable relationships with health outcomes and other types of adherence assessment have been shown in well-validated and rigorously developed self-report tools, namely Morisky Adherence Questionnaire 8 item (MMAS) (Morisky et al., 1986, Morisky et al., 2008, Voils et al., 2011). Utilising of multiple measures in adherence study can triangulate intervention effects through comparisons with one another (Stirratt et al., 2015, Velligan et al., 2010).

Dale et al. (2015) developed and evaluated a form of a mHealth intervention called "Text4Heart" aimed at improving adherence to cardio-protective behaviours in adults diagnosed with CHD. The investigators included medication taking, stopping smoking, physical activity, healthy eating, and limiting alcohol consumption as their target behaviours (as they were described by the authors).

A total of 123 CHD patients were identified by a trained researcher before discharge from 2 hospitals in Auckland, New Zealand. Participants were randomised to the intervention (n=61) or the control (n=62) group in a 1:1 ratio. The researchers supplied patients with a mobile phone for the duration of the trial. However, having access to the Internet was one of the requirements to participate in the study. This could be one of the limitations of the study that excluded those patients who did not have the Internet access.

In addition to usual care (i.e. Cardiac Rehabilitation), the intervention group received a 24-week mHealth programme. They received 7 daily TMs per week and had access to a supporting website. The frequency of TMs decreased over the period of the study. Between weeks 13 and 24, patients received 5 TMs per week. Intervention group also were given a pedometer to monitor their physical activity on their own. Investigators personalised TMs to patients' name and preferred time of day to receive TMs. Participants were asked to send their pedometer step counts on a weekly basis and to text in their questions or ask for feedback on other behaviours. Then, based on their achievement relating to the number of steps, they received automated responses. Their questions were answered individually by the study team within 2 days. Participants received reimbursement for any TM-related expenses.

Adherence to healthy lifestyle behaviours and medications was measured by a self-reported composite health behaviour score and Morisky questionnaire (MMAS) after 3 and 6 months from the study start point. Significantly higher medication adherence scores were reported by the intervention group compared to the control (mean difference: 0.58, 95% CI 0.19-0.97; P=0.004). The Text4Heart intervention showed a significant improvement in adherence to healthy behaviours at 3 months (Absolute Odds Ratio (AOR) 2.55, 95% CI 1.12-5.84; P=0.03), but not at 6 months (AOR 1.93, 95% CI 0.83-4.53; P=0.13). This can be related to the likelihood of occurring deterioration in unhealthy behaviours due to the decrease in the frequency of text messaging over time. With regards to the usability of two-way text messaging, it was reported that only 38% of participants texted in questions or comments to the research team (23/61). This low rate of patients' responses might be due to the anxiety and depression usually occur after hospital discharge from a cardiac event (Shemesh et al., 2009, Tully and Baker, 2012) that can have a negative

impact on patients' active involvement in such studies. The Study demonstrates the effectiveness of the intervention in this particular population in New Zealand; however, the findings cannot be generalisable to other populations or settings such as low and middle income countries. The Morisky instrument is used to measure medication adherence over time and would appear to be the instrument of choice for measuring adherence due to high reliability and validity.

Another similar parallel group, assessor-blinded RCT study was conducted by Kamal et al. (2015) among stroke survivors in Pakistan. The investigators sent automated SMS reminders to the intervention group for 2 months to improve medication adherence for stroke. Daily medication reminders were tailored to the participants' prescriptions. In addition, health-related information text messages were sent 2 times per week. The participants were required to reply to each SMS confirming whether they have taken or not taken their medicines. The costs of sending the text response were returned to the participants by giving them prepaid credit previously. Patients in control group did not receive any kind of the intervention. Their clinic appointments were reminded to both study groups couple of days before the due date via SMS and/or phone.

Two hundred Participants were randomly assigned to either intervention (n=100) or control group (n=100) in a 1:1 ratio with block size of 10. Medication adherence was measured at baseline and after 2 months using the Morisky questionnaire (MMAS). After 2 months, the intervention group showed a significant increase in medication adherence compared to the usual care group, mean difference was 0.54 (95 % CI; 0.22–0.85) (P=0.01). No report was found relating to the patients' response rate to the SMS reminders.

The investigators used a self-reported measure as the only adherence assessment tool that is highly dependent on patients' credibility in responding the adherence questions. Moreover, it was described by the authors that participants in the intervention group were disclosed to the reception of SMS and were well-instructed and seemed to be motivated to medication adherence compared to the control group. This may lead to inherent or performance bias that may artificially overestimate the adherence behaviour.

Almost all studies proposed SMS reminders as a scalable, cost-effective, widely available and attractive approach for patients after discharge from hospital to improve medication adherence. Although using two-way TM reminders as a form of mHealth intervention provided the possibility of communication between patients and providers, response rate in aforementioned studies showed lower interest in patients to reply text-messages. One of the reasons may be related to the text-messaging costs when participants are not reimbursed for such expenses. Moreover, some patients are only able to read TMs and they are not literate enough or competent to type and send TMs. Bidirectional TM reminders are highly relying on the active engagement of patients and providers. It also needs to be considered that many patients experience some degrees of anxiety and / or depression after hospital discharge from a cardiac event and prompting them to send reply messages may cause intrusion in their life as an additional source of stress (Shemesh et al., 2009, Tully and Baker, 2012). Having acknowledged limitations, caution is needed when asking patients to respond back to the TMs in mHealth studies. In the present study, one-way TM medication reminder was considered as a preferred mHealth intervention based on the findings from the survey study conducted in CHD patients prior to the trial.

3.5.3 mHealth Interventions other than TM reminder

One trial used a type of mHealth intervention other than text messaging. Vollmer et al. (2014) used a 2 Electronic Medical Record (EMR)-linked automated phone reminder for 1 year to improve adherence to cardiovascular medications in patients from 3 regions of the Kaiser Permanente (KP) health plan: Northwest, Hawaii, and Georgia in the USA.

In this study, 21,752 diabetic and/ or CVD patients aged 40 years and older and due or overdue for an Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ACEI/ARB) refill were recruited based on the study eligibility after being identified using EMRs of each region. Computer-generated randomisation assignments were stratified by region. All participants were randomised in a 1:1:1 ratio to receive either usual care (n=7255) or one of two

mHealth interventions, regular Interactive Voice Response (IVR) (n=7247) or enhanced IVR (n=7250).

Participants in usual care group received usual services offered in each region, including education and efforts to motivate Statin and ACEI/ARB medication taking. Regular IVR group received automated phone calls lasted 2 to 3 minutes to remind patients to refill ACEI/ARB prescriptions. Enhanced IVR involved automated phone calls plus personalised reminder letters (if a patient was 60-89 days overdue), a live outreach call (if a patient was more than 90 days overdue), EMR-based feedback to the primary care providers, their current BP report, cholesterol level and additional health-related informative mailed materials.

There were small but statistically significant improvements in ACEI/ARB adherence among both IVR interventions versus usual care, with OR for enhanced IVR of 1.21 (95% CI 1.10-1.32) and OR for regular IVR of 1.12 (95% CI 1.02-1.23) compared to usual care. The difference between enhanced and regular IVR groups was not statistically significant. Although the improvements were statistically significant within intervention groups, the overall effect was small. No significant changes reported in either Systolic BP or overall BP measures among subgroups.

Medication adherence was measured using the Medication Possession Ratio (MPR) at baseline and a modified version of PDC at the end of the study based on pharmacy records (as they were described by the authors). To calculate these measures, patient's prescribed medication's name, days supplied, and at least two fill dates are needed. However, there are two different formulas for each measure to find the final result (Choudhry et al., 2009). This indicated that there was an inconsistency between pre- and post-study adherence measurement and so the findings should be treated with caution.

It was mentioned by the authors as one of their study limitations that there was a considerable number of patients who were never reached by phone calls. This may be related to perceptions of patients towards the effectiveness versus intrusiveness of the IVR interventions that may have impact on their interests in receiving calls. It needs to be taken into consideration that patients who live in remote areas may have significant problems in receiving calls on their telephones. The call quality may be

often very poor to hear the voice. IVR or similar mHealth interventions using voice call reminders should be designed in recognition of mentioned limitations.

3.5.4 Comparing two mHealth Interventions

In these studies, 15% (2/13) compared the effect of two types of mHealth interventions on treatment adherence in their target population. Zolfaghari et al. (2012) conducted a quasi-experimental study for 3 months to evaluate and compare the effect of two mHealth interventions (SMS versus telephone calls) on improving HbA1c levels and adherence to treatment in Iranian diabetic patients.

Participants aged 18–65 years old were identified from the Iranian Diabetes Association. 80 eligible patients who had their own personal mobile phones were randomised by using a random number table and assigned to either SMS group (n=39) or telephone group (n=41).

The investigators sent 6 messages with maximum 160 characters per week (excluding weekends) to the SMS group providing information about healthy diet, physical activity, medication adherence, stress management and blood glucose self-monitoring. Here are two examples of messages relating to medication adherence:

Sample one: *“Please, consume your drugs at prescribed times”*;

Sample two: *“Take your recommended diabetic medication timely”*.

Participants in the telephone group received phone calls with the average length of 20 minutes per contact at least 2 times a week for the first month and once a week for the second and third month with the same contents as the SMS group.

HbA1C levels were assessed in patients' blood test and adherence was measured by a self-care diabetes questionnaire at the beginning, after 3 and 6 months of the study. There were significant improvements in HbA1C levels within SMS groups over the time of the study, with a mean change of -1.01 ; $SD\pm 0.01$ ($P<0.001$) and within telephone group with a mean change of -0.93 ; $SD\pm 0.13$ ($P<0.001$). Significant changes were reported in adherence to diabetes-related recommendations including medication taking comparing pre- and post-test results within SMS group with a mean change of 15.65 ; $SD\pm 2.72$ ($P<0.001$) and within the telephone group with a mean change of 21.46 ; $SD\pm 7.12$ ($P<0.001$). However, the study findings

showed that there were no statistically significant changes in HbA1C ($P=0.227$) and adherence to diabetes control recommendations including medication taking ($P=0.508$) between the two study groups. The absence of a non-intervention control group may reduce the power of the study in identifying the actual effect of the intervention on adherence to medication and other diabetes control recommendations.

It can be concluded from this study that SMS has the potential to be as effective as telephone follow-ups. Telephone follow-up relies on synchronous patient-provider communications. Studies reported that 15–27 per cent of patients were never reached by phone after several call attempts (Gray et al., 2010, Hwa and Wren, 2013). It also requires more time and labour such as a nurse or other health care staffs than the other methods to call and follow-up with patients (Armstrong et al., 2014, Zolfaghari et al., 2012). The delivery of predefined SMS messages can be obtained via an automated system regularly and without the necessity of extra programmes and time for clinical staff trainings (Bobrow et al., 2016). According to the findings of a systematic review conducted by Cutrona et al. (2010), person-independent interventions (delivered via electronic interface such as programmable reminders, or computer-generated personalised interventions) were the most successful mode of delivery for interventions to improve cardiovascular medication adherence rather than person-dependent interventions (non-automated). As it was described by Zolfaghari et al. (2012), in developing countries including Iran there is a shortage of nurses and health care providers. It seems that low-cost methods require less labour's efforts and so SMS-based mHealth intervention may have the potential to be designed and examined as an alternative method to address these issues.

In a more recent single-setting, three-arm RCT conducted by Bobrow et al. (2016) in South Africa, the effect of automated SMS-based adherence program (sent via an open-source web-based EMR system) on adult patients with hypertension was evaluated for 12 months. The investigators utilized two types of mHealth intervention to deliver BP-lowering medication adherence support including one-way versus two-way SMS texting.

Potential patients with high blood pressure aged 21 or older who had access to a mobile phone and could send SMS were identified by clinic staff in outpatient chronic disease services of a public clinic. A total of 1372 eligible patients were assigned to one of the three study groups, one-way SMS (n=457), interactive SMS (n=458), or usual care (n=457) using a web-based software algorithm in a 1:1:1 ratio. Research assistants (who collected data), statisticians, investigators and clinic staff were blinded to patients' allocation (as they were described by the authors). Although they were all trained to not ask patients about the types of SMS, patients might have discussed the text messages contents with the research team. This may have altered the blinding and affected the actual outcomes of the patients in the trial.

Participants allocated to the unidirectional SMS group received motivational weekly text-messages related to prescription refill and medication taking that contained educational information about high blood pressure and its treatment. The investigators also sent additional SMS messages to remind patients of clinic appointments or medications refill. Patients in the interactive SMS group were sent the same informative text-messages at weekly intervals as the one-way SMS group but could also reply to selected text-messages containing the request of free-to-user "Please-Call-Me". Participants in all randomised groups received non-health related SMS every six weeks.

Study primary outcomes including mean systolic BP (mean of the five systolic BP excluding the first reading), BP-lowering medication adherence (via calculating PDC based on pharmacy records) were measured at baseline and at 12 months.

It was found that mean SBP declined from the start-point to 12 months within all study groups. At the end-point of the study, the mean SBP changes in comparison with usual care was -2.2 mm Hg 95% CI (-4.4 to -0.040), with one-way SMS and -1.6 mm Hg 95% CI (-3.7 to 0.6) with tow-way SMS. The researchers did not report the difference in systolic BP measured between the study groups. This may reduce the power of the trial in terms of lack of the size of the study intervention effect.

The study showed a significant difference in the proportion of participants who had higher PDC in the one-way SMS group (62.8%) compared to usual care (49.4%) with $P < 0.001$, and in the interactive SMS group (59.7%) compared to usual care with

P=0.002. The measure of PDC used to assess adherence was based on pharmacy or clinic records that indicates dispensing in the clinic than the actual act of consuming medication by patients. Moreover, the investigators recruited a group of hypertensive patients rather than identifying those with poorly controlled BP. This may limit the extent to which BP improvement was possible.

The findings in this trial showed that one-way SMS might be as effective as interactive SMS in providing medication adherence support. It also provided evidence that automated adherence program delivered via either unidirectional or bidirectional text-messaging may have a small effect on BP control as a clinical outcome in comparison with usual care in hypertensive patients within a lower-resource setting. However, considering the acknowledged limitations in outcome measurements, caution is needed when interpreting the study findings.

3.6 Acceptability of mHealth Interventions

Slightly less than half of the studies (6/13) reported the acceptability and satisfaction of receiving mHealth intervention in their target study population.

In a study conducted by Strandbygaard et al. (2010) that evaluated the effect of 12-week passive daily TM on anti-asthmatic medication adherence in Denmark (see Section 3.5.1), no data were shown relating to the perception of participants towards receiving a daily SMS reminder. However, they discussed merely that participants in the intervention group perceived SMS reminders positively. They found that the majority of participants were not satisfy with SMS receiving time (10 am) that indicates improvement is needed in further studies. It may be useful to personalise the SMS timing to each participant to enhance the intervention effect, or survey patients prior to the study implementation to obtain their preferences regarding the delivery of mHealth intervention.

Quilici et al. (2013) who undertaken a study to examine the effect of one-month personalise6d unidirectional daily SMS reminders for aspirin intake in French ACS patients (see Section 3.5.1), provided a short general report of patients' feedback about the intervention. At the end of the study, it was found that 92% of participants were satisfied about receiving the intervention and believed the SMS

support program was valuable. The authors did not describe in detail how they collected the data relating to the patients' experience on receiving the intervention.

Similarly, in the TExT-MED study by Arora et al. (2014) that evaluated the effect of a one-way TM intervention on diabetic patients' self-care activities and medication adherence in Los Angeles County (see Section 3.5.1), program acceptability at the 6-month follow-up visit were explored. The satisfaction rate with the TExT-MED intervention was high (as they were reported by the authors). The majority of patients answered that they strongly agreed (25.5%)/ agreed (68.1%) that the TExT-MED was a good way to obtain information about diabetes. It was reported that participants in the intervention group enjoyed the TExT-MED (40.4% strongly agreed and 53.2% agreed). Slightly more than half of patients strongly agreed and around 37% agreed that the TMs' contents were easy-to-understand. As it was reported in the study, all of participants who received the TExT-MED intervention would recommend it to other diabetic patients. There was no particular information about the selection of the survey questions or the method used to obtain the survey data.

Park et al (2014) also evaluated the satisfaction of 53 CHD patients in Northern California who received personalised TM reminders after 30 days of the study by the Mobile Phone Use Questionnaire. The investigators developed the questionnaire specifically for the study to explore participants' experience with utilising mobile phone devices for medication reminders and/or receiving health-related information. It was reported by the authors that both experimental groups (reminders plus educational TMs and educational TM only) were highly satisfied with receiving the intervention. The majority of patients strongly agreed/ agreed that receiving TM for health and medication taking were helpful and promoted the feeling of being cared for. Although 88.6% strongly agreed/ agreed that the mobile phone-based TM intervention was easy-to-use, around 8% reported technical issues with receiving TM.

In another study, qualitative interviews were conducted by Vollmer et al. (2014) with participants and stakeholders of health plan including physicians, health leaders, managers, and pharmacists in 3 study sites in the US to obtain feedback to

the 12-month EMR-based automated cardiovascular medications phone reminders (see Section 3.5.3).

The investigators recruited stakeholders by email or letter, and an additional phone call, for open-ended, semi-structured interviews. An interview guide was developed to undertake interviews either in person or over the phone. A trained qualitative researcher analysed the transcribed interviews using content analysis. A survey also was conducted in 498 patients at the one-year follow-up to evaluate their satisfaction with the study intervention.

According to the study findings, around 70% of participants thought automated phone reminders were useful or very useful and 71% would like similar calls to be continued in the future. Seventy eight percent of the 379 participants who received enhanced IVR including additional informative mailed materials found the intervention useful or very useful, and would like to receive similar materials in the future.

Similar findings were found from in-depth qualitative interviews with 49 patients. Sixty three percent of interviewees perceived that phone calls were a useful service to help stay on track with their medication refills, and 31% thought the calls were valuable when getting older and forgetful. In this study, 57% of 30 respondents who received enhanced IVR reported that the mailing materials were useful in providing education and knowledge of the medication adherence importance. Ninety four percent of all interviewees believed the intervention should be carried on as a continuous service, and near 70% felt at least some of the mailings which were more personalised should be sustained.

Of 45 stakeholders interviewed, near 70% found the intervention as a helpful and important service for increasing medication adherence. It was reported by the authors that slightly less than half of the stakeholders thought the intervention was a proper utilisation of an inexpensive technology, and 27% believed that the intervention had the potential to provide outreach to patients who may slip through the cracks in different circumstances.

Another similar RCT conducted by Kamal et al. (2015) to examine automated interactive SMS reminders on improving medication adherence in Pakistanis stroke

survivors (see Section 3.5.2). After 2 months of the study, satisfaction and acceptability of the intervention were measured using specific tools that determined the effects and challenges of utilising this technology.

The investigators developed a self-reported questionnaire based on Roger's four attributes from the Diffusion of Innovations theory (Rogers, 2003) to identify the success of an innovation. The questionnaire reported satisfaction as percentage.

Roger's Diffusion Theory seeks to describe how innovations are adopted in a population (Rogers, 2003). As it was described by Robinson (2009), four attributes in the Diffusion Theory are:

- Simplicity that refers to the extent to which an innovation is thought as difficult-to-use;
- Compatibility is the second attribute that is defined as innovation consistency with the values, previous experiences, and potential users' needs;
- Observability of an innovation results that helps reduce the uncertainty in individuals; and
- Relative advantage of an innovation that may have an impact on the rate of innovation adoption by users.

The authors described that they also designed another questionnaire according to previous literature that measured satisfaction as proportions. Patients reported a high score satisfaction with intervention with a mean percentage of 96.07 %. In terms of Diffusion characteristics of mHealth intervention, the mean score was 95.6 % (7.6/8). The Roger's four attributes scores were 1.91/2, 1.91/2, 1.9/2 and 1.95/2 for simplicity, compatibility, observability and relative advantage, respectively.

To sum up, the majority of studies have established feasibility and high satisfaction with a mobile phone-based intervention among patients with chronic disease and in different settings. However, limited studies have been undertaken to assess mHealth acceptability in developing countries including Iran and there is still uncertainty in the existing body of knowledge. Therefore preliminary studies are needed focusing on the feasibility and acceptability of mHealth medication adherence interventions from patients and healthcare professionals' perspectives in developing countries prior to a definite RCT.

3.7 Theory-based mHealth Studies

Of thirteen studies selected for review, only 30% used a theory-based mHealth intervention to improve medication adherence. One of the importance of conducting a theory-based study is that it contributes to provide a framework for interventions development and evaluation (Abraham and Michie, 2008). This also assists in identifying the mediating-factors in behaviour change and the reasons for intervention success or failure (Lubans et al., 2008).

In the study conducted by Arora et al. (2014), the Health Belief Model of health behaviour (Janz and Becker, 1984) was applied in the development of a unidirectional TM-based mHealth intervention (TEXT-MED) for diabetic patients in the US. Based on this model, the intervention used in this 6-month trial emphasised education to impact on perceptions of patient with uncontrolled diabetes in favour of the appropriate health behaviour (i.e. improvement in HbA1C, medication adherence, self-efficacy and understanding of diabetes-related information) and used triggers to promote the desired action. As it was fully described in Section 3.5.1, the results demonstrated that at 6-month follow up the TEXT-MED did not significantly improve HbA1C in the intervention group compared to the usual care group.

In a study conducted in the US, Park et al. (2014) compared the effect of a 30-day interactive TM-based intervention on antiplatelet and statin adherence in three randomised groups (educational TM only, educational TMs plus reminders, No TM). The study intervention developed for patients with CHD, based on the Self-efficacy Theory (Bandura, 2004). As it was described by the authors, using TM medication reminders in combination with CHD –related educational TMs including self-care components may improve self-efficacy and confidence in patients to be adherent to their prescribed medication regimen. The two intervention groups showed higher adherence to antiplatelet medications compared to the control group, but not to Statins medications (see Section 3.5.2).

Similarly, Dale et al. (2015) developed automated daily bidirectional SMS-based intervention and a supporting website (Text4Heart) based on the principles of the Social Cognitive Theory (Bandura, 2004) and self-efficacy major mediators to promote change in lifestyle behaviours (quitting smoking, doing exercise, eating

healthy, and limiting alcohol-drink) in New Zealand patients with CHD. As it was described by the authors, the Common Sense Model (Cameron and Jago, 2008) was applied to develop the study intervention, as well. They used this model to provide coping strategies for changing patient perceptions and the harmful emotions that appear with a health threatening condition. The Text4Heart intervention group reported significant changes in adherence to healthy lifestyle behaviours compared to the usual care group at 3 months. However, the effect was not sustained at 6 months (see Section 3.5.2).

In Pakistan, Kamal et al. (2015) also developed and evaluated automated interactive SMS reminders based on the Health Belief Model and Social Cognitive Theory to improve medication adherence in stroke patients. SMS contents comprised of personalised medication reminders according to patients' prescriptions and health-related information specified by the Taxonomy of Behavioural Change for increasing physical activity and healthy eating (Michie et al., 2011). The investigators used the Health Belief Model in which behaviour change could be predicted based on multiple major determinants including perceived susceptibility, seriousness, advantages and obstacles of taking action, triggers to taking action and self-efficacy (Rosenstock, 1974, Rosenstock et al., 1988). It was described by the authors that SMS contents were developed according to these themes to encourage participants to change their behaviour. After 2 months, a significant improvement was found in medication adherence in patients who received SMS reminders compared to the control group (see Section 3.5.2). The results were an early report of the study findings (as they were described by the authors) and as such no data were available from which the sustainability of the intervention effect could be evaluated.

Limited mHealth interventions were developed by theory or frameworks that showed mixed results. This indicates that the mHealth studies have fallen short of attempting to explore the mechanisms of why the intervention would be effective or not, and be replicable in other research studies. Therefore, a need exists for research that develops an appropriate theory-based mHealth intervention and evaluates its effectiveness on improving medication adherence and the relevant health outcomes in CHD patients and in the particular setting of developing countries. In doing so, this PhD research sought to design and examine the effect of a mHealth medication

reminder intervention based on the principles of Bandura's Self-efficacy Theory and the World Health Organisation (WHO) Adherence Model (see Chapter 2).

3.8 Intervention Contents

While in designing the content of the reminder messages special considerations are required, the majority of the experimental studies do not provide detail required for reliably identifying intervention content. Reporting of intervention content in the selected studies for the literature review was brief and imprecise. For example, Akhu-Zaheya and Wa'ed, (2016) who evaluated the effect of SMS reminders on adherence to medication, diet and smoking cessation among adult cardiovascular patients in North of Jordan, provided an example of three types of text message templates about medications, healthy diet and smoking cessation (see Section 3.5.1). They did not describe the development process of the reminders' contents. Providing inadequate detail of intervention content limits the possibility of identifying the effective ingredients within the intervention.

In contrast, Arora et al. (2014), in their TExT-MED study on diabetic patients described that they developed some general, short (with maximum 160 character) and simple text messages through an iterative process; According to the authors, the development process comprised of combining 4 items including: (1) the National Diabetes Education Program materials; (2) multidisciplinary experts' opinions; (3) the target population's interests; and (4) findings from previous mHealth pilot study. The majority of participants in this study strongly agreed/ agreed that the TMs' contents were beneficial and easy-to-understand (see Section 3.5.1). This indicates the importance obtaining healthcare professionals' opinions and incorporating participants' feedback to generate message content (i.e. shared decision making) before its implementation to enhance the intervention effect.

The majority of the studies used general, short and simple SMS medication reminders that were more acceptable from the perspective of their recipients. For example, the SMS content in the study conducted by Kamal et al. (2015) among Pakistanis stroke patients (see Section 3.5.2) was:

“This is a reminder about your drug time. Please take your medicine. Have you taken your medicine? Reply with Yes or No.”

According to the authors, patients' survey showed a high score satisfaction with the intervention. Similarly, Park et al. (2014) who used interactive TM reminders among CHD patients in Northern California for 30 days received positive feedback from their study participants. An example of the medication reminder was:

‘John, take Plavix 75 mg at 9:00 AM. Respond with 1.’

Strandbygaard et al. (2010) delivered 12-week passive daily TM to asthmatic patients in Denmark (see Section 3.5.1) with the following content and participants reported high satisfaction with the intervention:

‘Remember to take your asthma medication morning and evening. From the Respiratory Unit’.

Since past studies that kept the content of the reminders straight-forward and simple have associated with greater patients' satisfaction, future studies should pay attention to these suggestions.

While SMS-based interventions have shown promise in improving adherence, it is not clear through which mechanisms they work. As it was described in Section 3.7, less than one third (4/13) of the studies (Arora et al., 2014, Dale et al., 2015, Kamal et al., 2015, Park et al., 2014) used a conceptual framework to develop the intervention content. In accordance with the Bandura's self-efficacy theory and the WHO adherence model (see Chapter 2), SMS messages may have the potential to positively influence adherence in three important ways. First, at the most basic level, SMS messages may serve as a pure reminder function to address forgetfulness (i.e. patient-related factor based on the WHO model). Second, the message content can provide social support/ persuasion (i.e. health system-related factor based on the WHO model) through reinforcement which in turn may increase patient's self-efficacy in taking medications especially during the early phase of hospital discharge, based on the Bandura's self-efficacy theory underlying this study. Third, reminders (as external cues/ triggers) can also make the importance of drug adherence more salient and tangible leading to the retention and sustainability of the medication taking behaviour. Considering the mechanisms in which SMS reminder interventions may influence medication adherence would be a helpful step for refining the intervention content on the basis of conceptual framework.

3.9 Discussion

Overall, based on the literature, mHealth approaches may have the potential to improve medication adherence in long-term conditions. However, there were some weaknesses and conflicting findings that became apparent in the review of the existing research presented in the literature. These included using self-reported measure as a single approach to assess medication adherence, conducting a small-scale trial with an insufficient follow-up period and sample size and lack of a conceptual framework in forming the study intervention. The number of studies on cardiac medication adherence is also limited. The majority of mHealth studies were also conducted in developed countries and as such cultural and economical differences must be acknowledged when considering the results. It was evident from the literature that although mHealth interventions showed promise in improving medication adherence in different patients, there is no consensus to identify which form of mHealth intervention were the most effective (Santo et al., 2016, Sarabi et al., 2016, Thakkar et al., 2015).

Despite being supported in the literature that nurses are well placed to encourage patients to be adherent to prescribed medications (Albert, 2008, Najafi et al., 2016, Stolic et al., 2010), most of the mHealth medication adherence interventions were evaluated by Medical Doctors. Patients may be unwilling to tell a doctor about missing doses and timing of the medications and how often and why they do not take the medication (Albert, 2008). The roles of nurses and medical doctors can be complementary, with nurses providing ongoing nursing interventions after discharge to encourage higher medication adherence (Bosworth, 2015, Larsen and Lutsep, 2013, Zolfaghari et al., 2012).

The majority of adherence interventions developed to address medication non-adherence focused on intentional non-adherence and their aims were to educate people and change their attitudes and beliefs (Haynes et al., 2008). However, even motivated people can forget; forgetfulness is the most common causes of unintentional non-adherence (Anderson, 2010, Clifford et al., 2008, Unni and Farris, 2011). There are limited studies that revealed expected results on patients' health outcomes and user satisfaction. With technology evolving rapidly, the use of older technologies such as beepers or pager systems are likely to decrease and new

technologies may arise. Currently, SMS reminders are increasingly being implemented in mHealth interventions aimed at improving adherence as mobile penetration is high globally. The effectiveness is influenced by patients' willingness to receive SMS reminders. The majority of included studies evaluating electronic reminders reported such interventions were well accepted by patients (see Section 3.6). There are, however, differences in the electronic reminders sent. Therefore, more studies are needed to investigate the influence of the content of reminder messages on adherence behaviour.

3.10 Conclusion and Rationale for the Study

Similar to any new innovation, mHealth for improving medication adherence in CHD patients is a work in progress. Knowledge and application of this new approach is on the rise in both developed and developing countries. However, there is a need of rigorous evidence from well-developed and implemented theory-based studies, focusing on patient's medication adherence self-efficacy and most common reasons to be non-adherent to treatment.

In Iran, medication adherence studies particularly using mHealth intervention among CR patients are limited. There is a need to understand and consider perceived patient barriers and their expectations in tailoring the design and implementation of such interventions (Toh et al., 2010, Nair et al., 2011, Almane et al., 2016). Intervention ease-of-use is one of the important aspects that reported as an ideal from the patients' perspective (Cutrona et al., 2010, Misono et al., 2010). The intervention needs to be developed to fit the patient and the cultural context (Lambert-Kerzner et al., 2012, Nieuwlaat et al., 2014). Difficulties in access to affordable mobile technologies or the knowledge to operate mobile devices are the criticism of mHealth (Dale et al., 2014).

The effectiveness of technology-based approaches in a particular setting of Cardiac Rehabilitation (CR) should be examined along multiple aspects: feasibility, acceptability, effectiveness, safety, user satisfaction, implementation and outcomes. Moreover, there is a lack of understanding regarding medication adherence and its assessment during CR programme. Typically the literature does not mention medicines when discussing CR (Packard et al., 2012). Educational interventions that

are offered during CR are less effective for those who unintentionally fail to adhere to medication (Touchette and Shapiro, 2008). Therefore, this study aimed to achieve an effective strategy to address medication non-adherence problem by sending triggers; in this case mobile phone reminders based on the principles of Bandura's Self-efficacy Theory and the WHO Adherence Model (see Chapter 2). The intervention focused on the most common patient-related factors (forgetfulness, carelessness and low self-efficacy), as well as healthcare system-related factors (patient- health care provider interaction and support) to improve patient medication adherence and health outcomes. This will assist nurses not only to improve interaction with patients after discharge from hospital, but also provide evidence based research regarding the most appropriate form of mHealth intervention implemented based on the MRC guideline for evaluating complex interventions (2013). The results from both qualitative and quantitative phases will also extend existing knowledge regarding the feasibility and acceptability of a mHealth cardiovascular medication adherence intervention in an Iranian setting.

CHAPTER 4: RESEARCH METHODOLOGY

The theoretical background and literature review in the preceding chapters revealed that poor adherence to medications and health recommendations among cardiovascular patients remain a significant issue for patients and healthcare providers in both developed and developing countries including Iran. With complex and changing medication regimens after hospital discharge among cardiac patients, innovative approaches such as mHealth may have the potential to improve medication adherence in the process of Cardiac Rehabilitation (CR) that have not been thoroughly investigated in Iran to date.

Technology-mediated interventions are usually not systematically developed, refined, or evaluated (Hoffmann et al., 2014, Moore et al., 2015). Using a systematic process in the development and evaluation of an innovative approach may be useful in identifying what is the process of any observed effect of an intervention, who and in which settings may benefit from such an intervention and who should deliver it; it also helps to inform and optimise the development, implementation and evaluation of further interventions (Moore et al., 2015). One of the helpful frameworks that have been proposed to address the issues in defining, developing, and evaluating interventions is the Medical Research Council (MRC) framework originally published in 2000 and updated in 2008 and 2013. The first version of MRC framework (2000) proposed a model comprised of different phases commonly applied in the evaluation of new medications from the first phase of preclinical research through to marketing stages. The updated MRC framework (2013) adjusts the previous model to a more flexible one with less linearity and greater focus on development and early piloting phase.

The research design for this study draws from the MRC framework (2013) that provides guidance on the development, evaluation and implementation of Randomised Control Trials (RCTs). Using the MRC framework, it appeared that a pilot mixed-method study would provide an appropriate design to refine and evaluate a previously developed mHealth intervention (from the master's study) to improve cardio-protective medication adherence based on the principles of Self-efficacy Theory within the context of the World Health Organisation (WHO)

Multidimensional Adherence Model. This study was undertaken to inform a future definitive multi-centre RCT.

4.1 Structure of the Methodology Chapter

In this Chapter, the methods and design of the study are described. A brief description of the MRC framework and rationale for a mixed-methods research approach are presented. The mixed-methods research paradigm and the philosophical assumptions underlying this approach are discussed, accordingly.

4.2 Aim and Objectives

The research aim of this mixed-methods study was:

- to develop and evaluate a nurse-led mHealth intervention to promote cardiovascular medication adherence in Iranian adult, male and female CR outpatients.

To achieve the research aim, the objectives of this research were defined based on each phase of the study using the MRC guideline:

Phase 1: Preclinical and Modelling Phase

1. to identify the pattern of ownership and utilisation of mobile phones in Iranian CHD patients;
2. to identify a preferable design for the study intervention based on CHD patients' opinions in Iran;
3. to explore Iranian cardiac nurses' perspectives of the potential effect of a mHealth intervention among Iranian CHD patients; and
4. to explore barriers and facilitators to implementation of the mHealth medication adherence intervention through which such interventions may affect cardiovascular medication adherence in an Iranian context.

Phase 2: Exploratory Trial Phase

5. to evaluate the effect of a 12-week mHealth intervention on medication adherence of Iranian male and female CHD patients participating in CR;
6. to evaluate the effect of a 12-week mHealth intervention on the secondary outcomes: Medication Adherence Self-Efficacy (MASE); cardiac Ejection Fraction (EF); cardiac Functional Capacity (FC); CHD-related

readmission/mortality rate and Health-related Quality of Life (HR-QOL) of Iranian male and female CHD patients participating in CR;

7. to explore the association between socio-demographic factors of the subjects and medication adherence in both intervention and control groups;
8. to explore the perception of participants in the intervention group towards the received mHealth intervention at the end of the study; and
9. to identify the recruitment and retention rate and inform the sample sizes required for a future definitive RCT.

4.3 Operational Definition

- **Cardiac Rehabilitation:** A hospital-based CR programme (Phase II) for CHD patients that usually occurs 4-6 weeks after discharge from the hospital setting.
- **CHD patients:** refers to all patients who attend the CR programme for the first time following discharge from hospital.
- **mHealth intervention:** A web-based software that sends written medication reminder (via text-message) to participant's mobile phones automatically at predefined times to remind medication taking.
- **Medication adherence:** refers to the scores of the self-reported Morisky Medication Adherence Scale (see Section 5.2.1): high adherence (≥ 8), medium adherence (6 to < 8) and low adherence (< 6).

4.4 Study Variables

All research projects are based around variables which are the characteristics or attributes of an individual, group, educational system, or the environment that is of interest in a research study and measured by study instruments (Polit and Beck, 2013). The independent and dependent variables for investigation in this study are presented in Table 4.1.

Table 4.1. Study variables

Independent Variables	Dependent Variables
mHealth Medication Reminders Intervention	Medication Adherence Level (Categorical)
	Medication Adherence Self-Efficacy (Numerical)
	Cardiac Ejection Fraction (EF) (Numerical)
	Cardiac Functional Capacity (FC) (Categorical)
	CHD-related Readmission/Mortality Rate (Categorical)
	Health-related Quality of Life (HR-QOL) (Numerical)

4.5 Medical Research Council (MRC) Framework

The MRC framework for the development and evaluation of RCTs, suggests a phased approach that includes both quantitative and qualitative methodologies (2013). In this study, to develop and evaluate the mHealth intervention, a mixed-methods approach was considered in which quantitative and qualitative studies are combined. More specifically, an “embedded design” was used (Clark and Creswell, 2011). This design is characterised by adding a qualitative strand within a quantitative design in order to enhance the overall design to address the primary purpose of the study (Clark and Creswell, 2011). The MRC framework entails a recursive process of development, feasibility and pilot testing, evaluation and implementation of the intervention. Hence, before any formal efficacy assessment can be performed, comprehensive preparatory work is conducted (Senn et al., 2013). The original model of the MRC comprised an investigative sequence of five phases:

- First, theory and evidence are assessed in order to provisionally identify the steps and the key components of the intervention (Preclinical Phase).
- Second, an understanding of the intervention and its possible effects is developed (Phase I: The modelling phase).
- Third, the feasibility of key components is assessed, and the recruitment procedures and measurements of outcomes are tested (Phase II: The exploratory trial phase).

- Fourth, RCTs are conducted to evaluate the impact of the complex intervention. These trials require adequate power, adequate randomisation, appropriate outcome measures and other standard features of well-designed trials (Phase III: the definitive RCT).
- Finally, separate studies are conducted to establish the long-term and real-life effectiveness of the intervention (Phase IV: the long-term implementation).

Figure 4.1 provides a phased process of the development, evaluation, and implementation of interventions and RCTs, according to the MRC framework (2013).

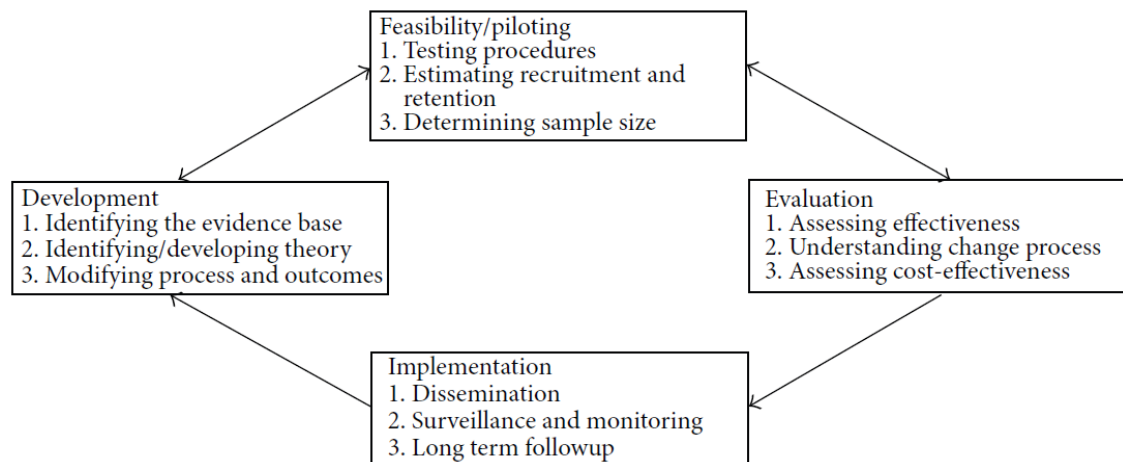


Figure 4.1. A phased process of the development, evaluation, and implementation of interventions and RCTs, according to the MRC framework (2013, p. 589)

This study focuses around the first 2 stages of the MRC framework to refine and evaluate a mHealth medication adherence intervention; Phase I as part of the preclinical and modelling phase consisted of three stages: (1) exploring a relevant theory (Chapter 2) and identifying evidence base (Chapter 3), (2) conducting a self-completion survey among Iranian CHD patients (3) conducting qualitative focus groups with participation of Iranian cardiac nurses in order to tailor the intervention to the local context. Findings from the study phase 1 informed the second phase (i.e. Exploratory Trial). A logic model is provided to present key steps and the activities required for each step based on the MRC framework adapted from Corry et al. (2013) (see Figure 4.2).

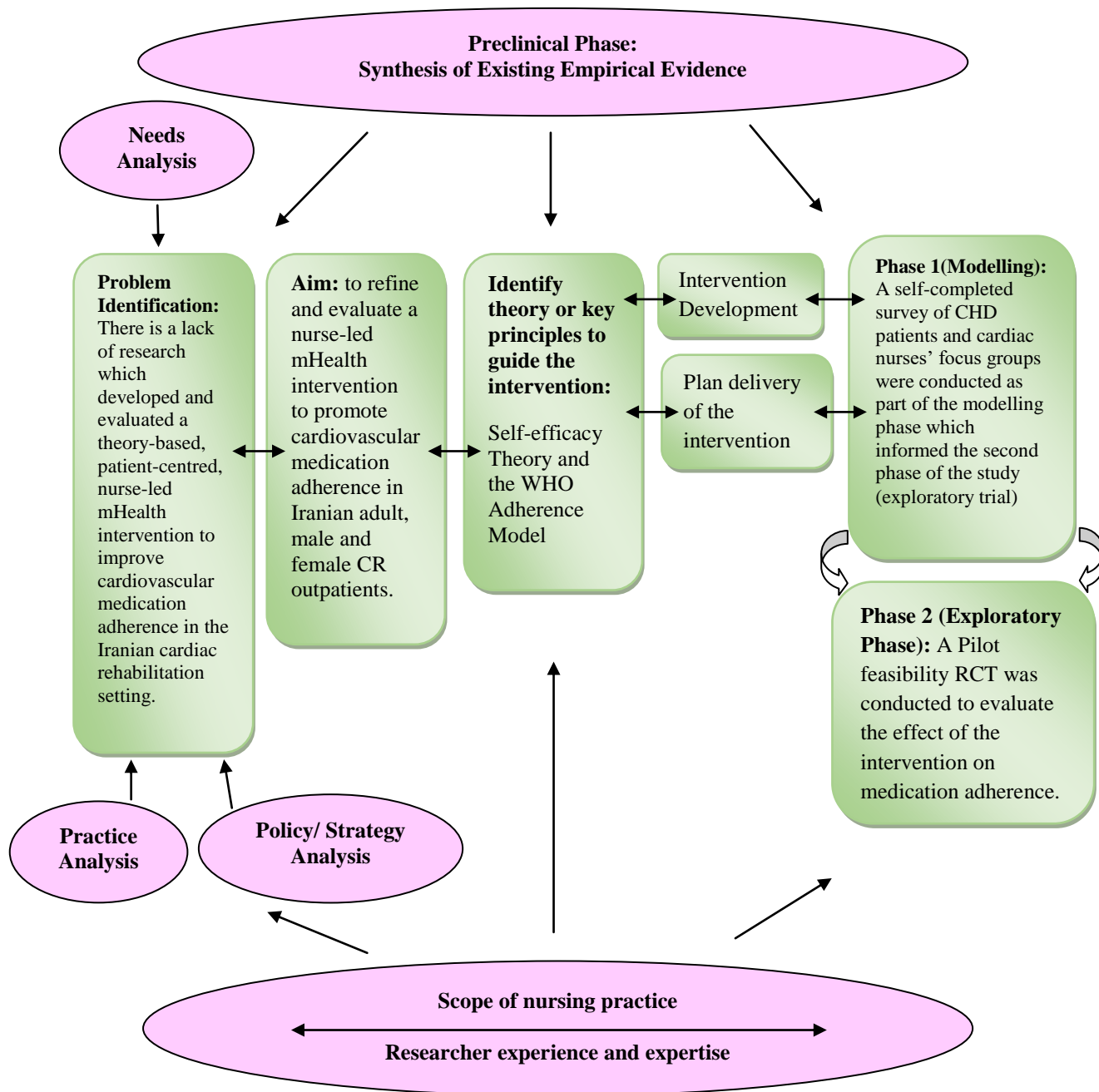


Figure 4.2. Logic model for developing and evaluating a nurse-led mHealth intervention based on the MRC framework adapted from Corry et al. (2013)

4.5.1 Preclinical and Modelling (Phase 1)

During the first phase of the study, a theoretical background and evidence base relating to the issue of medication non-adherence among CHD patients and the effectiveness of mHealth intervention for this group of patients were reviewed (see Chapter 3). Details on the use of the self-efficacy theory and the WHO adherence model as well as identifying the evidence base to inform the development of a nurse-led mHealth medication adherence intervention for Iranian CHD patients have been presented in Chapters 2 and 3.

A self-completion survey study was undertaken to identify the pattern of ownership and utilisation of mobile phones among Iranian CHD patients; and to explore a preferable design for the study intervention from Iranian CHD patients' perspective (objectives 1 and 2). Then, Focus Group Discussions (FGDs) were conducted to explore Iranian cardiac nurses' views and their experiences about mHealth intervention (objectives 3 and 4) (see Section 4.2).

4.5.2 Exploratory Trial (Phase 2)

Phase II included a 12-week pilot RCT (pre-test, post-test parallel group design experiment) to evaluate the mHealth intervention in terms of its effect on cardiovascular medication adherence (primary outcome) and secondary outcomes among CHD patients in an Iranian CR setting, recruitment, retention, acceptability, and to inform the sample sizes required for a larger more definitive RCT (Objectives 5-9) (see Section 4.2).

4.6 Method Rational

A mixed-methods design, so called the third research paradigm, was chosen as an appropriate method in this study since it was helpful to bridge the schism between quantitative and qualitative research in order to refine and evaluate a mHealth intervention to promote cardiovascular medication adherence, based on the MRC framework (Onwuegbuzie and Leech, 2005, Creswell, 2013). Philosophically, it is the third research movement that moves past the paradigm wars by offering a logical and practical alternative (Johnson and Onwuegbuzie, 2004). Mixed-methods' logic of inquiry includes the use of induction (or discovery of patterns), deduction (testing of theories and hypotheses), and abduction (uncovering and relying on the best of a

set of explanations for understanding one's results) (Creswell, 2013). Mixed methods research also is an attempt to legitimate the use of multiple approaches in answering research questions. Research methods should follow research questions in a way that offers the best chance to obtain useful answers. Many research questions and combinations of questions are best and most fully answered through mixed research solutions (Creswell, 2013, Johnson and Onwuegbuzie, 2004).

Although the desire of all forms of human research and inquiry is to understand and make sense of the world, a distinction has traditionally been made between quantitative and qualitative methods (McEvoy and Richards, 2006). Qualitative approaches (in this study: qualitative focus groups) are associated with the constructivist paradigm identifying the lived experience or beliefs of social actors (in this study: Iranian CHD patients and cardiac nurses) (Blaikie, 2009). Quantitative approaches (in this study: pilot RCT) that incorporate standardised measures and statistical techniques are usually associated with a positivist paradigm that is linked with the natural sciences (Creswell, 2013, McEvoy and Richards, 2006). It is believed that pragmatism is the best philosophical basis of mixed-methods research; according to the methodological pragmatists, neither quantitative nor qualitative methods alone are sufficient to develop a complete analysis (Johnson and Onwuegbuzie, 2004, Tashakkori and Teddlie, 2010). Therefore, they need to be used in combination, so that they can complement each other (Creswell, 2013).

In the fields of health and social research the use of mixed-method approaches is widely advocated (Creswell, 2013, Johnson and Onwuegbuzie, 2004, Tashakkori and Teddlie, 2010). Johnson and Onwuegbuzie (2004) provided a concise and clear list of the advantages and disadvantages of mixed-methods research that is presented in Table 4.2.

A mixed-methods approach employs strategies of inquiry that involve collecting data either simultaneously or sequentially to best understand research problems (Creswell, 2013). The data collection also involves gathering both numeric information as well as non-numeric information so that the final database represents both quantitative and qualitative information (Creswell, 2013, Fetters et al., 2013).

Key rationale for combining quantitative and qualitative methods is:

1. seeking convergence and confirmation of results from various approaches studying the same problem (triangulation);
2. results from one method could be used to elaborate on results from the other method (complementarities);
3. results from one method could be used to develop or inform the other method (development);
4. results from one method could be reshaped to questions or results from the other method (initiation); and
5. the range of inquiry could be extended by using different methods for different inquiry components (expansion) (Hanson et al., 2005, Fetters et al., 2013).

Table 4.2. Strengths and Weaknesses of Mixed Research (Johnson and Onwuegbuzie, 2004, p.21)

Strengths	Weaknesses
<ul style="list-style-type: none"> ✓ Words, pictures, and narrative can be used to add meaning to numbers ✓ Numbers can be used to add precision to words, pictures, and narrative ✓ Provides quantitative and qualitative research strengths ✓ The researcher may generate and test a grounded theory ✓ Answers a broader and more complete range of research questions because the researcher is not confined to a single method or approach ✓ In a two-stage sequential design, the Stage 1 results can be used to develop and inform the purpose and design of the Stage 2 component ✓ The researcher can use the strengths of an additional method to overcome the weaknesses in another method by using both methods in one research study ✓ Can provide stronger evidence for a conclusion through the convergence and corroboration of findings ✓ Can add insights and understanding that might be missed when only a single method is used ✓ Can be used to increase the generalisability the results ✓ Produces more complete knowledge 	<ul style="list-style-type: none"> ○ Can be difficult for a single researcher to carry out both qualitative and quantitative research, especially if two or more approaches are expected to be used concurrently; it may require a research team ○ The researcher has to learn about multiple methods and approaches and understand how to mix them appropriately ○ Methodological purists contend that one should always work solely within either a qualitative or a quantitative paradigm. ○ More expensive ○ More time consuming. ○ Some of the details of conducting mixed research remain to be worked out fully by research methodologists

In this multi-stage developmental mixed-methods study, results from qualitative method of cardiac nurses' focus groups and descriptive CHD patients' survey helped to develop and inform the quantitative method of pilot RCT. Also the study rationale is in accord with Punch (2013) who suggested that mixed-methods investigations may be used to better understand a research problem by converging numeric trends from quantitative data and specific details from qualitative data.

4.6.1 Rational for Conducting Survey in the Quantitative Stage

This research study employed a descriptive self-completion survey of CHD patients along with the qualitative focus groups in the modelling phase to inform the pilot RCT. Survey research is among popular research designs in health studies, although it has roots in social research with positivist theoretical perspective within objectivist epistemology (Polit and Beck, 2013).

Surveys are a non-experimental research strategy designed to estimate certain parameters or provide information about the prevalence, dispersion, and associations of variables in the selection of a large sample of individuals from a predefined population (Polit and Beck, 2013, Rea and Parker, 2014). According to Polit and Beck (2013), in general methodology the word survey only covers quantitative studies that primarily aim at describing numerical distributions of variables (e.g. prevalence rates) in the population.

Most survey analyses are inductive, neither iterative and not multi-source nor very sophisticated theoretically. It is, first of all, a simple research design, not for the study of social structures and processes but for the study of diversity in a population (Jansen, 2010). In this study, descriptive information from the survey questionnaire identified and quantified the data regarding key factors that would influence the feasibility and acceptability of using mobile phones as an adherence aid for CHD patients receiving cardio-protective medications in an Iranian setting.

One of the advantages of survey research is to provide data based on real-world experiences (Polit and Beck, 2013). The breadth of inclusion of many individuals (e.g. hospitalised male and female CHD patients) shows that this method allows researchers to gather data, based on a representative sample, and can therefore address issues of generalisability in a more efficient way than other

approaches (Rea and Parker, 2014). Surveys are not expensive and provide a vast range of data for many purposes in a short period of time (Polit and Beck, 2013). Surveys are very useful when exploring topics that are difficult to access using other strategies and mostly rely on self-reporting (Jansen, 2010, Rea and Parker, 2014). Considering these factors, a self-completion survey was chosen as a part of the overall mixed-methods embedded design to describe the ownership and usage of mobile phones among Iranian CHD patients and their expectations/ preferences towards a mobile phone-based medication adherence intervention. Using the survey results, the researcher was able to further refine the mHealth intervention and evaluate it utilising a pilot RCT involving Iranian CHD patients during their CR programme.

4.6.2 Rational for Conducting Focus Groups in the Qualitative Stage

In this mixed-methods study, qualitative focus groups were conducted to produce data to complement the data from the patients' survey in the modelling phase, to inform the pilot RCT. Focus groups have been used by researchers in many qualitative research traditions and in the study of health problems (Polit and Beck, 2004). They can play a particularly important role in obtaining the viewpoints of many individuals in a short time (Kidd and Parshall, 2000).

Focus group sessions are carefully planned discussions that take advantage of group dynamics for accessing rich information in an efficient manner (Polit and Beck, 2004). Moreover, focus groups capitalise on the fact that members react to what is being said by others, thereby potentially leading to richer or deeper expressions of opinion (Polit and Beck, 2004). Also, focus group interviews are usually stimulating to respondents rather than either self-administered open-ended surveys or structured group interviews with less spontaneous interaction (Bristol and Fern, 1996). Focus group members comment on each other's point of view, often challenging each other's motives and actions in a real discussion (Kidd and Parshall, 2000). Studies of focus groups have shown that they are similar to individual interviews in terms of number or quality of ideas generated (Kidd and Parshall, 2000).

In this study, focus groups aimed to explore cardiac nurses' perception (as professional bodies that have close relationships with their patients) towards developing a nurse-led mHealth medication reminder intervention and its potential effect on medication adherence among Iranian CHD patients. The study focus was primarily on nurses' experience of using mHealth, their potential role and the possible challenges in developing and delivering the study intervention to CHD patients in an Iranian context. Taken together with the lack of knowledge surrounding mHealth among healthcare professionals as well as the little mHealth improvement on the delivery of health care in Iran, conducting focus groups helped the researcher to obtain a thorough understanding of practicality and acceptability of the mHealth medication adherence interventions, from the perspective of nursing staff and across their levels of experience.

Focus group findings together with information obtained from patients' survey were used to understand how a mHealth medication adherence intervention would be appropriate in the Iranian context. This knowledge was essential to developing a feasible and acceptable mHealth intervention.

4.6.3 Rational for Conducting Pilot RCT in the Quantitative Stage

Since this research used a quantitative-dominant mixed-methods approach with a focus on the pilot RCT as the core component, it is important to explore what an RCT is. An RCT is a type of evaluation that seeks to determine whether an intervention resulted to the intended effect on study participants (Polit and Beck, 2013).

Elements of true experiments are manipulation, control, random assignment, and random selection (Polit and Beck, 2013). The most important of these elements are manipulation and control. Manipulation means an action which is purposefully implemented by the researcher in the environment; The action is termed "an experimental treatment/ intervention" and is the independent variable within the study (Houser, 2013). In this study, a mHealth medication adherence intervention is the experimental intervention (see Section 5.1.1). Independent and dependent variables are presented in Table 4.1.

Control is used to prevent outside factors from influencing the study outcome (Houser, 2013). When something is manipulated and controlled and then the outcome happens, it makes the researcher more confident that the manipulation “caused” the outcome (Polit and Beck, 2004). Moreover, highly controlled nature of the experimental study and its systematic conduct eliminates error and bias and enhances researcher’s confidence that the manipulation “caused” the outcome (Houser, 2013). One method of applying such control is through the use of a control group that is not subjected to the independent variable. In the hospital setting, there is not a total absence of the care relating to the experimental intervention, consequently control group is subjected to routine conventional interventions (i.e.usual care). In this study, the control group received the usual care in order to contribute to evaluate the effect of the mHealth-delivered medication reminders.

Random assignment is another essential element of a true experiment (Polit and Beck, 2004). The procedure of random assignment means that participants are randomly assigned to the study groups or interventions if there are different groups or interventions in the study. This indicates that participants have an equal chance of getting into all of the groups in an experiment regardless of who the study individual is. The advantage of this process is that the researcher is confident about homogeneity of the groups or treatments at the beginning of the study so that there is more certainty that the manipulation (experimental intervention) “caused” the outcome and this also prevent selection bias (Parahoo, 2014).

In choosing an appropriate design to meet the aim of the second phase of the study (i.e. exploratory trial), the researcher considered to incorporate manipulation, control and randomisation. These factors considered, a RCT design was deemed to be appropriate for the quantitative part of the study.

A pilot trial briefly refers to a small background research study for helping to inform a further confirmatory study (Arain et al., 2010). Large RCTs often take place in multiple settings and involve the integrated efforts of different investigators, research directors, healthcare professionals, and patients (Whitehead et al., 2014). A pilot trial can operate as a test, simulation or a safeguard for investigators and

funding bodies to provide an assurance that larger trials are developed in an optimal level and can be implemented in practice (Arnold et al., 2009).

There are a variety of objectives in conducting a randomised pilot trial including a study of feasibility, an assessment of the inclusion and exclusion criteria and recruitment efficiency for a further RCT, and/or an evaluation of outcome measures (Arain et al., 2010, Arnold et al., 2009, Whitehead et al., 2014). For example, in the present study, the feasibility of undertaking a definitive RCT evaluated in a pilot RCT that simulated different aspects of the larger trial of the mHealth medication reminder intervention in an Iranian context, from the recruitment process to measurement of outcomes and data collection (Whitehead et al., 2014).

Overall, pilot study findings can provide invaluable awareness into the potential determinants and issues of a study protocol for a future definitive RCTs. Table 4.3 summarises the advantages and disadvantages of pilot trials adapted from a study by Arnold et al. (2009).

Table 4.3. Advantages and disadvantages of pilot studies adapted from Arnold et al. (2009, p. S73)

	Advantages	Disadvantages
Feasibility	✓ Pilot trials can predict the feasibility and acceptability of protocol implementation in a future trial	○ Feasibility and acceptability assessments may be misleading if only a small number of highly motivated, non-representative centres participate
Sample size requirement	✓ Objectives of pilot trials focused on feasibility can often be met with relatively few patients	○ Pilot trial results are unlikely to provide reliable estimates of the sample size required for the full trial
Cost	✓ Pilot trials help to ensure that financial investments in large trials are allocated responsibly	○ Complex pilot trials can be expensive relative to their yield
Estimates of harm (patient safety)	✓ Large trials of potentially harmful interventions may be averted by a pilot trial clearly demonstrating harm	○ Pilot trials are rarely powered to confidently detect harm with respect to clinically important outcomes
Estimates of benefit	✓ Reporting a threshold signal of a surrogate outcome may be justified when examining mechanisms	○ By design, pilot trials are usually underpowered to determine reliable estimates of effect on clinically important outcomes

Using the MRC framework, in the second phase of this study or as a quantitative part of this mixed-methods research, a pilot RCT was conducted to evaluate the feasibility and acceptability of the mHealth intervention in an Iranian CR setting to inform a full-scale RCT (see Section 5.3).

4.7 Mixed-Methods Research Paradigm

Paradigms refer to beliefs patterns or philosophical assumptions which are characterised by ontology (the nature of reality), epistemology (the nature of knowledge) and methodologies are used to study a phenomena (Weaver and Olson, 2006).

A third perspective of reality appeared in the Ancient World, but different from Plato/ Socrates (singular or universal truths or approaches to viewing the world) and the Sophists (multiple or relative truths). Mixed-methods research has been given a position between the extremes Plato (quantitative research) and the Sophists (qualitative research), with mixed research seeking to value both of these viewpoints' wisdom while also attempting a useful middle solution for various issues (research) of interest (Johnson et al., 2007). According to Teddlie and Tashakkori (2010), Aristotle (384-322 B.C.) who used both deductive (i.e. the process of reasoning from a general logic) and inductive reasoning (using particular measurable facts to reach a general conclusion) in his research has been considered a mixed methodologist. Aristotle's principle of the "golden mean" that refers to balancing ideological extremes reflects a pragmatist paradigm underlying many modern mixed-methods approaches (Johnson et al., 2007). Pragmatism is a philosophical tradition in which the truth of a hypothesis, based on inductive reasoning and constant empirical verification, is in continual transformation and revised when new findings are identified (Tashakkori and Teddlie, 2010).

A major assumption of this study was that neither a quantitative nor qualitative approach used alone could capture the significant factors that play a role in refining and evaluating a mHealth medication adherence intervention. It was assumed that results from focus groups qualitative study (with interpretivist-constructivist assumption) and descriptive CHD patients' survey would help to refine the mHealth medication adherence intervention (to make it appropriate to the Iranian context) and

inform the pilot RCT (with positivist assumption). Although this research used the mixed-method research strategy (i.e., using heterogeneous paradigms between quantitative and qualitative research), the quantitative research was dominant as the research core component. Therefore, the main paradigm of this research was based on the quantitative research paradigm. Quantitative assumptions are in line with positivist paradigm in which social observations should be considered as entities in the same way that physical scientists deal with physical phenomena (Tuli, 2011).

4.7.1 Epistemological Considerations

For positivists that are emerged mostly from 19th century, scientific explanation is the main purpose of research (Tuli, 2011). From a positivist perspective, social science is seen as a formulated approach for integrating deductive reasoning into precise empirical findings related to individual's behaviour in order to explore and confirm a group of plausible causal laws that can be applied to make predictions about common models of human activity (Creswell, 2013). A primary assumption of this paradigm is that the science goal is to establish the most objective approaches possible to achieve the most accurate reality approximation (Tuli, 2011). Researchers who conduct a study from this point of view describes in quantitative terms how variables interact, form events, and lead to outcomes; these explanations are often developed and tested in experimental studies (Creswell, 2013).

In the present study, following the refinement and modification of the mHealth intervention in order to make it appropriate to the Iranian context, based on the cardiac nurses' opinions and CHD patients' preferences (i.e. modelling phase), it was important to pilot the intervention among CR patients. For this reason, a positivist perspective offered a useful theoretical lens through which the effect of a nurse-led mHealth intervention on improving medication adherence among CHD patients in an Iranian CR setting was examined.

4.7.2 Ontological Considerations

The nature of reality is the ontological concerns in social science research (Creswell, 2013, Tuli, 2011). An investigator with a positivist views perceives reality as being "out there" in the world that needs to be explored using objective ways (Tuli, 2011). They believe in "objectivism" that assumes that there is an independent

reality (Tashakkori and Teddlie, 2010). Research findings are often described in a quantitative form, in figures that speak for themselves (Tashakkori and Teddlie, 2010, Tuli, 2011).

The main reason of using realist/objectivist ontology in this research was to focus on variables measurement (e.g. medication adherence). It was also helpful to measure the intervention effects, especially through group changes. In this way, the data collection approaches mainly focused on collecting hard data (i.e. in the form of numbers) to allow evidence to be demonstrated quantitatively.

4.8 Reliability, Validity and Rigour

It is the researchers' responsibility to make a significant effort to obtain systematic, reliable, coherent and transparent research outcomes. This research study comprised both quantitative and qualitative research strategies. Reliability and validity in quantitative and trustworthiness in qualitative research play an important role in ensuring the quality of the research (Parahoo, 2014).

According to Polit and Beck (2008), validity (or internal validity) that mainly concerns the soundness of the study's evidence refers to the "*degree to which inferences made in a study are accurate and well-founded*"(p.768). In qualitative research, this usually refers to "*how well the research represents the actual phenomenon*"(Morse, 2015, p.19) .

Reliability is defined as the "*accuracy and consistency of information obtained in a study*" (Polit and Beck, 2008, p.196). It usually concerns the ability to achieve the same findings if the researcher repeats the study (Morse, 2015). In medical and nursing researches, the concern is no longer related to the value of the research methods but it is about ensuring or enhancing the reliability and validity (Creswell, 2013).

In assessing the quality of quantitative research, there are checklists that play a crucial role such as the CONSORT – CONSolidated Standards Of Reporting Trials (see Appendix 1). They provide guidance on important queries that need to be asked to help those unfamiliar with this method to evaluate or review quantitative works and in reminding researchers of the need for a quality approach. In this study, the researcher adhered to the CONSORT (2010) guideline to conduct and report the

quantitative research portion of this study (i.e. pilot RCT). The reliability and validity of all research instruments (i.e. questionnaires) used in this study are reported in Section 5.3.

Both criteria of reliability and validity are important to obtain rigor (also called trustworthiness) in qualitative research (Morse, 2015). To ensure the rigor of the qualitative data, Lincoln and Guba's Evaluation Criteria, including creditability, dependability, transferability, and conformability, was used (Speziale et al., 2011).

For creditability of findings, the prolonged involvement of the researcher with the research and data and member checking (i.e. the transcribed interviews were emailed to the participants to obtain verification of information accuracy) were done. Maximum variations in age, experience of the participants, and type of cardiology ward worked by the nurses also helped to increase the credibility of data.

In qualitative inquiry, transferability (i.e. generalisability) refers to the application of the findings to another situation or population (Speziale et al., 2011). The over-reaching research goal was not to establish precise cause and effect relationships regarding which factors contribute to changes in medication adherence. Quantitative data analysis procedures, such as multiple logistic regressions, were used to examine tentative relationships between patients' socio-demographic characteristics and self-reported medication adherence. The qualitative data were mainly used to inform the exploratory trial phase. The focus of the research was on potential transferability of the findings, not on generalisability since the study was conducted among specific group of patients (i.e. CHD patients) and in a specific context (i.e. an Iranian CR setting). For transferability of findings, important quotes and socio-demographic characteristics of the nurses were reported.

Conformability was also assessed by two experts familiar with qualitative research in addition to the main researcher; they reviewed the transcripts independently and confirmed the coding and categories and checked the researcher's interpretations. For dependability, the researcher provided enough information and reported the research process so that other researchers will be able to follow-up the research.

4.9 Summary

This chapter has introduced and critiqued the rationale to select a multi-stage developmental mixed-methods design. Based on the MRC framework, both quantitative and qualitative data used in two phase (modelling and exploratory trial) to refine and evaluate the nurse-led mHealth intervention on improving cardiovascular medication adherence in an Iranian CR setting. The effect of the study intervention was best understood by using a combination of both qualitative and quantitative data; however, the quantitative pilot RCT was the core component of this study. Additionally, a developmental quantitative-dominant mixed-methods design underpinned by positivist epistemology and objective ontology was selected because results from qualitative nurses' focus groups and descriptive CHD patients' survey (undertaken in modelling phase) were used to develop and inform the quantitative pilot RCT of the mHealth intervention. Moreover, this mixed method research has attempted to assure the reliability and validity of quantitative study via statistical strategies and the rigour and quality of qualitative study by considering Lincoln and Guba's Evaluation Criteria. In the following chapter, research methods, procedures undertaken for data collection and data analysis as well as ethical considerations will be presented.

CHAPTER 5: METHODS, DATA COLLECTION AND ANALYSIS

The aim of this chapter is to provide a description of the methods for implementation of the patients' perception survey, qualitative focus groups and pilot RCT of the mixed-methods study. The procedure for sample recruitment, study setting, negotiation access and procedure for collection of the data, data collection instruments, and methods of data analysis used in each study are described. A visual model of procedures used in this mixed-methods study is displayed. The research permission and ethical considerations pertinent to this study are also discussed.

A description of the refinement and evaluation of the previously developed mHealth intervention (Khonsari et al., 2015) used in this study to promote the cardio-protective medication adherence among CHD patients in an Iranian CR setting, using the first 2 phases of the MRC framework is provided. The work reported here was done to inform the design of an intervention that will be tested in a future definitive RCT. Table 5.1 summarises the refinement and evaluation of the intervention through the stages of the MRC framework process.

Table 5.1. Studies undertaken based on the phases of the MRC framework (2013)

Study stages based on the MRC framework	Studies undertaken
1. Preclinical/ Modelling Phase:	
1.1 Identifying Evidence Base and Exploration of Relevant Theory	<ul style="list-style-type: none"> • Reviewed the background information and epidemiological evidence related to CVD, CHD, CR, medication adherence among patients suffering from CHD and mHealth with a particular focus on the Iranian context; • Reviewed existing evidence and theories related to medication adherence to identify an appropriate theory and behaviour change techniques; • Improved understanding of the issue of non-adherence among cardiovascular patients and previous interventions that enhanced adherence in different chronic conditions including CHD through identifying and reviewing existing literature.
1.2 Modelling process	<ul style="list-style-type: none"> • Self-completed survey was conducted to identify the pattern of ownership and utilisation of mobile phones and a preferable design for the intervention, based on Iranian CHD patients' opinions;

-
- Qualitative study with Iranian cardiac nurses was conducted to refine the intervention content. This included focus groups with nurses (who would deliver the intervention) to explore their perspectives about the potential effect of a mHealth intervention among Iranian CHD patients; and to determine barriers and facilitators to implementation of the mHealth medication adherence intervention through which such interventions may affect cardiovascular medication adherence in the Iranian context.
-

2. Exploratory Trial Phase (Assessing feasibility and piloting methods)

2.1 Pilot-testing the study procedure, preliminary intervention, its delivery and acceptability

- Tested the intervention for feasibility and acceptability and final adaptation of the intervention through conducting a 12-week pilot trial of the intervention in the Iranian CR setting
- Self-completed survey was conducted at the end of the pilot trial to explore the perception of participants in the intervention group towards the received mHealth intervention

2.2 Estimating recruitment and retention and identifying any potential barriers to these

- Recruitment through outpatient CR clinic to identify the effectiveness of the method.
- Pilot trial over 12 weeks to estimate the recruitment and retention rate.

2.3 Determining sample size by anticipating the effect sizes in a pilot study

- Identifying the effect of the intervention on the primary outcome of the study (i.e. medication adherence) to inform the sample sizes required for a further larger trial
-

Prior to presenting each phase of the study, it is important to provide a description related to the mHealth intervention used in this study.

5.1 mHealth Medication Adherence Intervention

A mobile phone/ mHealth medication adherence intervention has been developed in 2013 as part of the researcher's master project (see Section 1.6). The intervention effectiveness was piloted among Acute Coronary Syndrome (ACS) patients in Malaysia that showed significant results (Khonsari et al., 2015). Theoretically, in this PhD, the same intervention was remodeled and modified based on the dimensions of medication adherence suggested by the WHO and principles of the Bandura' Self-efficacy Theory (see Chapter Two) and then piloted among adults male and female CHD patients in an Iranian CR setting.

Methodologically, the Medical Research Council (MRC) framework was used as a guide to refine and evaluate the study intervention and to inform a future definitive RCT. The intervention was refined after exploring the perspectives of both Iranian CHD patients (by conducting a cross-sectional survey) and experienced cardiac nurses (by conducting focus group discussions) about potential effects and challenges of mHealth implementation and then piloted for the first time among Iranian CR patients.

In the present study, a multi-stage mixed-methods design was used to refine and evaluate the mHealth intervention on cardiovascular medication adherence. The evaluation of qualitative and quantitative data improved and tailored the intervention to the local context and ensured it could be applied to this group of patients.

In this PhD, the researcher evaluated the effect of the mHealth intervention on a variety of self-reported and objective outcomes among CHD patients over the period of 12 weeks. For example, the effect of the SMS reminders was examined on patients' self-efficacy in taking their prescribed cardiovascular medications over the study time period, cardiac Ejection Fraction and Health-Related Quality of Life (HRQoL) as a sensitive outcome variable within and between the study groups (i.e. usual care vs. usual care plus SMS medication reminders) (see Section 5.3). These outcomes were not evaluated in the previous study.

5.1.1 Components of the Study Intervention

The mHealth intervention used in this study was software with no specific hardware dependency, thus offered maximum portability and ease of use. The system consisted of various parts that were responsible for gathering and managing the information related to the patients and their medications, storing data, scheduling, sending text messages and recording delivery reports (see Picture 5.1). All these tasks were managed automatically to minimise the manual effort. It also provided additional features such as query, advanced search and generating report that were exportable to many standard formats. Picture 5.2 demonstrates an image of the software search page.

Reminders
Sent SMS
Subjects
Logout

TABLE: Subjects

Search

Search (*) Show all Advanced Search

Exact phrase All words Any word

ID	Name (*)	Age	Sex	Date Of Birth	Mobile Number (*)	Admission Date	Discharge Date	Hospital LOS						
83		50	Male	1344	00	21/2/2016	21/4/2016	5						
84		53	Female		00	21/2/2016	21/4/2016	9						
85		46	Female		0090	21/2/2016	21/4/2016	7						
86		57	Female		00	21/2/2016	21/4/2016	15						
87		63	Female	1331	00	21/2/2016	21/4/2016	7						
88		69	Male		00	21/2/2016	21/4/2016	30						
89		40	Male	1355	00	21/2/2016	21/4/2016	20						
90		59	Male		009	21/2/2016	21/4/2016	7						
91		66	Male	1328	009	21/2/2016	21/4/2016	4						
92		60	Male		00	21/2/2016	21/4/2016	7						
93		63	Male		009	21/2/2016	21/4/2016	7						
99		62	Male		0096	21/2/2016	21/4/2016	7						
100		84	Male		00	21/2/2016	21/4/2016	2						
101		41	Female		009	21/2/2016	21/4/2016	2						

TABLE: Reminders (1 Records)

ID	Subject ID	Medicine Name	Start Date	End Date	Refill Date
183	93		22/2/2016	22/4/2016	22/4/2016

Picture 5.1. Patients' information and scheduled text message reminders

Reminders
Sent SMS
Subjects
Logout

Search TABLE: Subjects

[Back to List](#)

ID	=	
Name	contains	
Age	=	
Sex	=	<input checked="" type="radio"/> Male <input type="radio"/> Female
Date Of Birth	=	
Mobile Number	contains	
Telephone Number	contains	
Address	contains	
Diagnosis	=	STEMI
Admission Date	=	06/04/2016
Discharge Date	=	
Hospital LOS	=	
Marital Status	=	Married
Race	=	Other
Educational Level	=	Secondary
Employed	=	<input type="radio"/> Yes <input type="radio"/> No
Financial Resource	=	Self Sponsored
Income	=	
Living Arrangement	=	With Friends
NO Daily Medications	=	
Diabetes	=	<input type="checkbox"/>
Hypertension	=	<input type="checkbox"/>
Hyperlipidemia	=	<input type="checkbox"/>
Other Info	contains	

Search Reset

April, 2016

wk	Sun	Mon	Tue	Wed	Thu	Fri	Sat
12						1	2
13	3	4	5	6	7	8	9
14	10	11	12	13	14	15	16
15	17	18	19	20	21	22	23
16	24	25	26	27	28	29	30

Wed, Apr 20

Picture 5.2. Software search page

In terms of the intervention workflow, the first step was to add patient data and notifications. The scheduler service then executed the SMS sender program at pre-scheduled times. It would in turn access the patient information database to generate correspondent text messages according to the desired template as well as notification data. Finally, a connection to an external SMS gateway was established to send generated messages. The SMS sender program was also responsible for collecting delivery reports and updating the database. To sum up, the intervention comprised of delivering automated daily medication reminders based on a predefined template, starting from the date of patient's recruitment. Figure 5.1 shows the intervention work flow diagram.

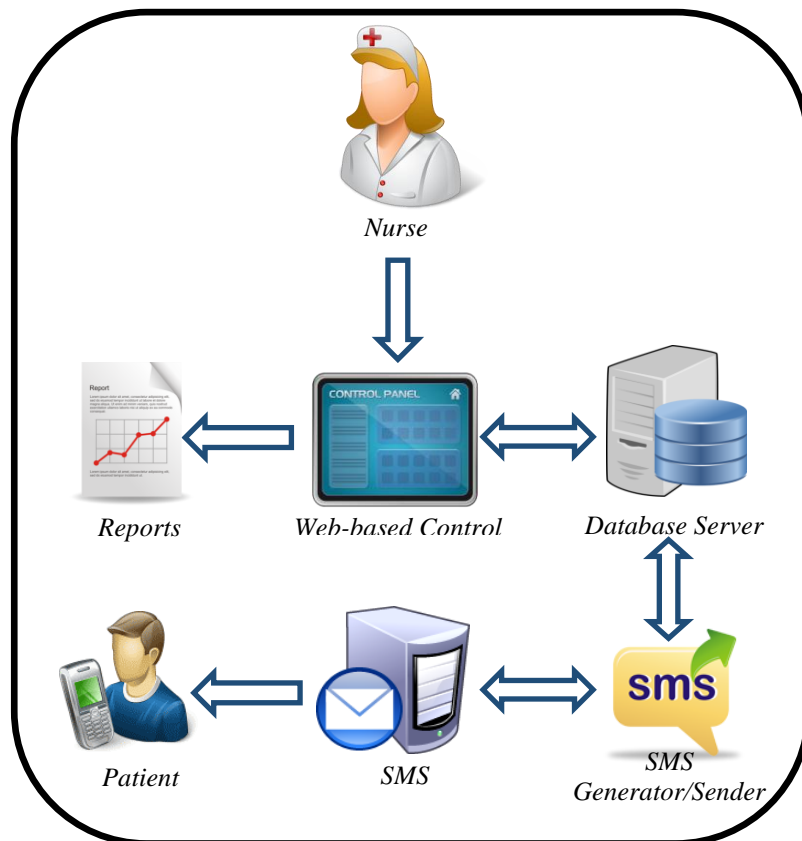


Figure 5.1. The intervention work flow

Intervention components were demonstrated to participants at recruitment. All participants were informed to not respond to the reminder text messages since the text message delivery status was captured by the online web-based interface for each

participant. The length and number of characters in the reminder message were short and the content was simple and easy to understand. When the course of medication was completed, a message was sent reminding patients to have their prescribed cardioprotective medications refilled.

Frequency, timing, content and the method of the delivering medication reminders were finalised based on the findings from the first phase of the study (see Section 6.1.3) to support patients remember taking their newly prescribed cardioprotective medications, prevent forgetfulness and carelessness and improve medication adherence self-efficacy. The major element of the intervention involved medication adherence enhancement together with consequent improvement in the study secondary outcomes (i.e. Medication Adherence Self-Efficacy (MASE); cardiac Ejection Fraction (EF); cardiac Functional Capacity (FC); CHD-related readmission/mortality rate and Health-related Quality of Life (HR-QOL)).

Table 5.2 presents some examples of reminder contents based on the principles of the study theoretical frameworks.

Table 5.2. Reminders 'objectives and contents

Study Stage	Message Objective	Example
Pilot Trial (12 weeks)	<p><i>Based on the Self-efficacy Theory:</i></p> <ul style="list-style-type: none"> ▪ To promote patient's self-efficacy in taking their newly prescribed medications via sending automated daily reminders (as a form of social support from a healthcare provider) to their mobile phones <p><i>Based on the WHO Adherence Model:</i></p> <ul style="list-style-type: none"> ▪ To prevent forgetfulness, carelessness and promote self-efficacy (patient-related factors) ▪ To maintain patient-provider connection and provide social support (system-related factor) 	<i>"Please don't forget to take your medications".</i>
Medications out of supply	To remind patient of having prescription refilled	<i>"Please don't forget to refill prescription".</i>

To validate the stability and reliability of the intervention functioning in Iran, text messages were sent two times daily (10am and 10pm) to four healthy volunteers with different mobile phones and different mobile phone providers over a one-week period. Volunteers were asked to keep their mobile phones charged and turned on

throughout this one-week intervention stability assessment. Participants were asked to send a reply back at the time of receipt of the text message when it arrived on their mobile phones. 100% of text messages were successfully delivered to volunteers' mobile phones.

5.2 Phase 1 - Study 1 & 2 (Preclinical/ Modelling)

The first phase of the study as part of the preclinical/ modelling phase started with a comprehensive literature review. The background information and epidemiological evidence related to CVD, CHD, CR, medication adherence among patients suffering from CHD and mHealth with a particular focus on the Iranian context were reviewed. Next, existing evidence and theories related to medication adherence to identify an appropriate theory and behaviour change techniques were identified. A thorough understanding of the issue of non-adherence among cardiovascular patients and previous interventions that enhanced adherence in different chronic conditions was achieved through identifying and reviewing existing literature. Background information, details on the use of the self-efficacy theory and the WHO adherence model as well as identifying the evidence base to inform the development of a nurse-led mHealth medication adherence intervention for Iranian CHD patients have been presented in Chapters 1-3.

During the first phase of the study, a self-completed survey of CHD patients and cardiac nurses' focus groups were conducted to inform the second phase of the study (exploratory trial).

5.2.1 Study 1 - Patients' Perception Survey

A self-completion survey conducted among male and female CHD patients, aged 18 and over in one hospital affiliated to Tehran University of Medical Sciences. The study setting provides routine cardiovascular treatment and support to patients in Tehran, the capital city of Iran. CHD patients attend the outpatient CR clinic approximately 3 times in a week for the hospital-based exercise and routine follow-up visits with the physician (see Section 1.2.1).

Specifically, the survey aimed to identify:

- the pattern of ownership, utilisation of mobile phones in Iranian CHD patients (Objective 1); and
- a preferable design for the study intervention based on CHD patients' opinions in Iran (Objective 2).

Sample and Setting

123 male and female patients aged 18 years and over with primary diagnosis of CHD (Myocardial Infarction (MI), angina or revascularisation) presented at CR clinic were recruited by the researcher (SKh) and asked to complete the survey independently before starting their exercise programme. On average, the CR clinic has over 100 new admissions per month for a 24-session exercise programme. The convenience sample included all eligible participants. Patients were excluded if they had developmental or cognitive disabilities that impacted on their ability to provide informed consent, or if they did not have the physical capacity to provide informed consent. The study was conducted over a period of three weeks in September 2015. CHD patients recruited from outpatient CR clinic of an educational research and medical centre for cardiovascular disease affiliated to Tehran University of Medical Sciences with 420 beds dedicated to the diagnosis and therapy of coronary and heart diseases. About 360,000 outpatients, 16,000 heart surgery and 50,000 angiography and angioplasties have taken place in this centre in recent five years (Tehran Heart Centre, 2015). It is one of the largest referral centres for heart bypass surgery in Iran in which almost more than 3500 heart surgeries (3000 cases of coronary and 500 cases of valve and congenital surgeries) are carried out every year.

Procedure

The researcher (SKh) met with the CR Clinic Manager (MN) and the CR Head Nurse (MS) regarding the study after receiving ethical approval and permission letter from the hospital (i.e. the study setting) (see also 5.4). Both were satisfied with the ethical approval and all permissions granted by the Ethics Committees of the hospital, Tehran University and the university where the researcher was based and gave permission for this convenience sample of samples to be approached.

The researcher and the CR Clinic Manager arranged a mutually suitable day and time for the researcher to attend the CR clinic. The 132 subjects attending the CR clinic were informed of the study by the Clinic Manager following their first out-patient CR appointment. Of 132 subjects, 123 (see Section 6.1.1) consented and agreed to complete the questionnaire (see 5.3.2) and were subsequently introduced to the researcher in a side-room of the clinic. The researcher provided an explanation of the purpose of the study and instruction on completion of the questionnaire. Confidentiality was assured to all participants with the understanding that they could withdraw at any time. Participants then completed the questionnaire and returned it to the researcher on leaving.

Data Collection

The survey instruments were:

- A socio-demographic questionnaire (see Appendix 3):

Socio-demographic factors such as age, gender, education level, marital status, employment, living arrangement, monthly income and receiving health insurance services were asked to be completed by patients.

- Electronic Supplementary Material adapted for use from a similar study (Shet et al., 2010) (see Appendix 4):

The survey questionnaire completed by the patients during a face-to-face visit and consisted of 21 items that covered two main domains of enquiry; what is the pattern of ownership and use of mobile phones among CHD patients; what might a patient-preferred design for a mobile phone-based intervention to influence medication adherence look like. Respondents were briefed that there was no right or wrong answer and they chose the best answer for each question based on their personal experience/ preferences. The context established by the questionnaire and the wording of questions have important effects on how questions are understood and answered by the individual respondents (Polit and Beck, 2013). Therefore, the questionnaire as a survey instrument should be designed precisely. It means that in the process of preparing the questionnaire, the researcher should maintain the focus of the study objectives and clear conception of the research problem and the

population of interest (Engel and Schutt, 2012). The questionnaire should be considered as a structured tool, in which each part and every single question deliver a clear purpose in association with research objectives and each part correlates other parts (Polit and Beck, 2013). By considering these points, the survey questionnaire of this study was translated into the local language and back-translated into English, then piloted initially in the hospital clinic following which the validity of the responses were reviewed, and questions edited as necessary. Two experts with clinical and scientific expertise (one was a Professor in Nursing and the other one was a Critical Care Nurse Specialist) to help validate the translated questionnaire. Content validity of this instrument was evaluated by calculating an Average Content Validity Index at the summary score level (S-CVI/Ave). The S-CVI/Ave is the average of the proportion of items that received a 'relevant' rating by the experts (Waltz, 2005). The S-CVI /Ave of the survey questionnaire were 0.9 (see Appendix 5). As the generally accepted cut-off is 0.9 or higher (Waltz, 2005), the content validity of the survey instrument was deemed to be acceptable. Based on the experts' opinion, item 1 was replaced by item 3. Questions 6 and 6a were removed to prevent survey complexity.

- Morisky Self-Reported Medication Adherence Scale (Appendix 6):

Measuring the adherence of patients could be a challenging problem for clinicians. There are different tools to determine adherence to medications. One of the reliable and widely used scales in this regard is the 8-item Morisky Medication Adherence Scale (MMAS-8) (Morisky et al., 2008). The 8-item scale with a reliability of 0.83 and good concurrent and predictive validity is a self-report questionnaire (with good predictive validity in patients at risk of cardiovascular disease) to assess medication-taking behaviour and adherence (Morisky and DiMatteo, 2011, Morisky et al., 2008). This measure has been found to positively correlate with pharmacy fills (Continuous Single-interval Medication Availability (CSA), Medication Possession Ratio (MPR), and Continuous Multiple-interval Medication Gaps (CMG) was $\geq 75\%$) (Krousel-Wood et al., 2009).

Since its introduction, the MMAS-8 has been studied in different conditions and languages including Persian (Moharamzad et al., 2015). Internal consistency of

the Persian-version of the MMAS-8 reported using Cronbach's α coefficient that was 0.697 and the test-retest reliability showed satisfactory reliability and stability of the instrument with Spearman's rank correlation coefficient of 0.940 ($P < 0.001$) (Moharamzad et al., 2015). Regarding the known groups' comparison, the results showed that the Persian MMAS-8, has an acceptable construct validity (Moharamzad et al., 2015). Overall, the Persian-version of the MMAS is a reliable and valid tool for Persian-speaking patients for using in cardiac conditions as well as other disciplines to study medication adherence in other chronic conditions which necessitate long-term taking of medication(s) by the suffering patient (Moharamzad et al., 2015).

This instrument measures non-adherence to medications due to the reasons like forgetfulness, carelessness, feeling better, or feeling worse (AlGhurair et al., 2012). According to the literature, there is no "gold standard" to measure the medication adherence behaviour (Jimmy and Jose, 2011, Ho et al., 2009). The most common indirect methods are the patient's self-report that is simple, inexpensive and the most practical method in the clinical setting and represented the standard practice (Jimmy and Jose, 2011). The questionnaire was completed by all participants. The validated Persian translation of the MMAS-8 had been asked from Prof. Donald E. Morisky, the owner of this scale, as well as permission to use the scale in this study (see Appendix 7).

- Short Form Health Survey Version 2.0 (SF-12v2) (Appendix 8)

The concept of Health-Related Quality of Life (HRQoL) is regarded as a sensitive outcome variable in health outcome measurement studies (Anderson and Burckhardt, 1999). HRQoL is a multidimensional concept that refers to function and well-being on various dimensions of health, including physical, emotional, social and spiritual aspects of life (Anderson and Burckhardt, 1999, King and Hinds, 2011) The SF-12v2® Health Survey (Fleishman et al., 2010, Ware et al., 2002) is a brief, generic, well-tested instrument used worldwide that was developed from the 36-item SF-36v2® Health Survey (Ware Jr, 2000). The SF-12v2 is a multi-purpose Short Form (SF) generic measure of health status that uses a Likert scale format and is used to measure eight domains of HRQOL (Ware et al., 2002). In the survey study, the

standard four-week recall period version was used. The SF-12v2 is comprised of a 12-item subset of the SF-36 version 2 (SF-36v2) categorised in eight domains: Bodily Pain (BP), General Health (GH), Vitality (VT), and Social Functioning (SF) with one item each. In addition, Physical Functioning (PF), Mental Health (MH), Role Physical (RP), and Role Emotional (RE) domains are represented with two items each (Ware et al., 2002). The information obtained from the eight health domain scales is then aggregated to provide summary measures of the respondent's physical and mental health. The internal consistency reliability of the SF-12v2 estimates 0.91 for the physical (Physical Component Summary/ PCS) and 0.87 for the Mental Component Summary (MCS) measures. When used with one or more disease-specific measures, the SF-12v2 provides information that can help evaluate patients with common chronic conditions (in this case, CHD), as well as monitor and compare their outcomes over time. Since its introduction, the SF-12v2 has been studied in different conditions and languages including Persian (Montazeri et al., 2011). Regarding the reliability of the Persian-version of the SF-12v2, the results showed that both summary measures (PCS-12 and MCS-12) exceeded the 0.70 level for Cronbach's alpha indicating satisfactory results (0.87 and 0.82 respectively) (Montazeri et al., 2011). Known-groups comparison showed that the SF-12v2 discriminated well between subgroups of people who differed in their health condition; this supports that construct validity of the scale is acceptable (Montazeri et al., 2011). Overall, the SF-12v2 is a reliable and valid measure of HRQoL among Iranians and could be used in health outcome studies (Montazeri et al., 2011). The questionnaires were completed by all survey participants. The validated Persian translation of the SF-12v2 and permission to use was asked from the QualityMetric Inc. (License Number: QM029383) (see Appendix 9).

Data Analysis

All data were analysed using the computer program Statistical Packages for Social Sciences (SPSS) version 21. The significance level in this study is $\alpha=0.05$. Both descriptive and inferential analysis were carried out using SPSS.

Quantitative/ statistical analysis, in this survey study, comprised of sufficient data screening methods to identify miscoded and missing data, descriptive and

inferential analysis. The raw data obtained during the data collection period were coded in preparation for analysis. Data processing was undertaken through the utilisation of a previously prepared codebook. The codebook was developed to provide not only the codes associated with the various values given to the study variables, but also the codes given to data which required transformations in order that statistical analyses could be carried out. Following processing, data were verified for errors and corrected prior to the execution of any statistical analyses. Screening procedures assisted the researcher in optimising data so that the analysis procedure produced the most accurate and efficient estimates (Pallant and Manual, 2007).

After cleaning data, frequencies and percentages were used to present detailed information on nominal and ordinal (categorical) data (such as gender, marital status, educational level, employment status, mobile phone ownership). Mean and Standard Deviation (SD) were used to describe continuous variables such as age, length of hospital stay, and number of daily medications. Categories of data were also presented in tables or graphs to provide a pictorial description of the sample, the use of descriptive statistics to further describe individual variables, and the use of statistical analysis for the purpose of looking for relationships among categories or variables (Polit and Beck, 2004, Wood and Ross-Kerr, 2010).

5.2.2 Study 2 - Focus Groups

Qualitative focus groups were conducted among 23 male and female nurse staff with at least six months work experience in cardiology or/ and CR wards, in three hospitals affiliated to Tehran University of Medical Sciences. Principal Nurse Supervisors/ Matrons in the study sites were asked to invite potential participants, provide a brief explanation of the study to nurses and arrange a date and venue for the Focus Group Discussions (FGDs).

FGDs specific objectives were to explore:

- Iranian cardiac nurses' perspectives about the potential effect of a mHealth intervention among Iranian CHD patients (Objective 3); and
- Potential barriers and facilitators to implementation of the mHealth medication adherence intervention through which such interventions may

affect cardiovascular medication adherence in an Iranian context (Objective 4).

Sample and Setting

According to Kidd and Parshall (2000), for purposes of peer-reviewed social and health research, confidence in focus group findings almost always can be enhanced by conducting multiple groups (ideally from multiple sites) and by including other data sources. Therefore, the researcher (SKh) asked the gatekeepers (i.e. Principal Nurse Supervisors/ Matrons) in each study site (i.e. two heart centres and one tertiary hospital affiliated to Tehran University of Medical Sciences) to invite cardiac nurses verbally from CR clinics and arrange a date and venue for the focus group discussions. There was a range of 7-10 staff nurse working in CR clinic of each study site. Of those invited through the gatekeepers (the number was not recorded), 23 male and female nurse staff were recruited.

Two Cardiovascular, Medical and Research Centres were considered as study settings for the focus groups, these were among the largest specialist and subspecialist centres in the Middle East. One is the same location in which the survey was conducted. The other one, with a total of 601 beds served, 70 hospitalisations, 20 surgical operations, 80 Catheterisation Laboratory procedures, and 40 Electrophysiology procedures on an average daily basis. The Centre currently enjoys the services of over 1700 staff members, 92 full-time medical faculty members, and 169 residents, specialist fellows, and subspecialist fellows in various cardiovascular disciplines. The third study site is a tertiary hospital in the centre of Tehran with a capacity of about 1400 hospital beds. The centre has faculty staff (n=270), nursing staff (n=1103), medical students (n=97), residents (n=402), subspecialty trainees (n=110) and stagers (n=135). There was a total number of 870,000 patients were admitted and approximately 31,000 surgeries were conducted in that hospital in 2010.

Data Collection

Before the start of the FGDs, the researcher introduced the study, highlighting its purpose, objectives, procedures, and expected outcomes. A short socio-

demographic questionnaire (Appendix 10) was provided for each participant at the beginning of each session.

An interview guide was developed to structure FGDs (Appendix 11). However, while a structured protocol was employed to guide FGDs, all responses were open-ended and the discussions were flexible allowing pursuit of issues raised by the participants that were not in the original FGD protocol. Specifically, participants were asked to reflect on (1) their experience with applying mHealth (2) positive and negative aspects of mHealth (3) challenges of using mHealth for patients and healthcare providers (4) strategies for best implementing a mHealth-based intervention to improve cardiac medication adherence.

The focus groups were conducted in the native language of participants, which was typically Farsi. They were conducted and facilitated by the researcher (SKh) in three different days in November 2015. All focus groups were audio-recorded with permission from participants and transcribed verbatim after each session. The average interview time was fifty minutes (minimum 40 minutes and maximum 60 minutes). As a validity check, the researcher asked participants to verify a verbal summary of the key points (Krueger and Casey, 2014).

Data Analysis

Qualitative data were analysed for all focus groups. Data analysis involved an initial reading of the three focus group transcripts. The methods used to code and categorise focus group data were adapted from approaches to qualitative content analysis discussed by Graneheim and Lundman (2004). Following steps have been taken to interpret the data:

The transcript was read and brief notes were taken in the margin when interesting or relevant information was found. After that, the notes made in the margins were reviewed and the different types of information were listed. The next step was to read the list and categorise each item in a way that offered a description of what it was about. Then it was identified whether or not the categories can be linked anyway and they were listed as major or minor categories. At this stage, the various major and minor categories were compared and contrasted. Finally, all of the categories were reviewed and it was ascertained whether some categories can be

merged or if some need to then be sub-categorised. All original transcripts were reviewed and all steps were taken several times to ensure that all the information that needs to be categorised has been so.

The main researcher (SKh) identified themes that emerged from the data for cardiac nurses. ARN (Professor in nursing) and BKh (Master's in nursing) independently analysed one fourth of the scripts (different scripts for each person) to identify themes for each of the three focus groups. There was a high level of agreement between the researchers on the nature of the themes.

5.3 Phase 2 - Study 3 (Exploratory Trial)

A two-arm (parallel), pretest-posttest pilot RCT with an equivalent comparison group was conducted among male and female adult Iranian CR patients of one Cardiovascular, Medical and Research Centre affiliated to Tehran University of Medical Sciences. This study was conducted between February and April 2016. The intervention group received automated timely mHealth medication reminders based on a predefined template every morning (This pattern was defined according to the phase I study findings), starting from the date of patient's recruitment for 12 weeks. The 12 weeks of the intervention was selected as it takes approximately 10 weeks (based on daily repetition) for participants to adopt new behaviours (in this case, medication taking) (Gardner et al., 2012). Moreover, between one and three months after discharge is when cardiac patients are most susceptible of discontinuation of their medications (Airoldi et al., 2007, Balaguer-Malfagón et al., 2006, Park et al., 2014).

Pilot RCT specific objectives were to:

- to evaluate the effect of a 12-week mHealth intervention on medication adherence of Iranian male and female CHD patients participating in CR (Objective 5);
- to evaluate the effect of a 12-week mHealth intervention on the secondary outcomes: Medication Adherence Self-Efficacy (MASE); cardiac Ejection Fraction (EF); cardiac Functional Capacity (FC); CHD-related readmission/mortality rate and Health-related Quality of Life (HR-QOL) of Iranian male and female CHD patients participating in CR (Objective 6);

- to explore the association between socio-demographic factors of the subjects and medication adherence in both intervention and control groups (Objective 7);
- to explore the perception of participants in the intervention group towards the received mHealth intervention at the end of the study (Objective 8); and
- to identify the recruitment and retention rate and inform the sample sizes required for a further larger trial (Objective 9).

Study Sample and Setting

CHD patients were recruited from an educational research and medical centre for cardiovascular disease affiliated to Tehran University of Medical Sciences, the same place in which the survey and one of the FGDs were conducted. A convenience sample of newly diagnosed CHD patients was recruited by the researcher. Eligible participants were Iranian male and female adults (ages 18 years and older) with a documented diagnosis of CHD (Myocardial Infarction (MI), angina or revascularisation) who met the criteria for usual CR care and had at least a basic mobile phone to receive text messages. Exclusion criteria were (a) unwilling to participate in the study; (b) being illiterate for reading reminders; (c) not being available for the 12 weeks period of the study (including being unavailable by phone and/or travelling out of the country), (d) being diagnosed with a level of cognitive impairment such that the process of informed consent may be obscured, (e) being physically unwell or diagnoses with a terminal illness.

Sample size

A major reason for conducting the pilot study was to determine initial data for the primary outcome measure (e.g. medication adherence), in order to perform a sample size calculation for a larger definitive RCT (Lancaster et al., 2004). Setting an appropriate sample size for any study is important. If a study is too large it may be judged to be unethical as participants may be unnecessarily exposed to risks and burdens (Thabane et al., 2010). There is the additional issue that setting the sample size too high may lead to a preventable failure to reach the recruitment target (Lancaster et al., 2004). A sample size that is too small will have an imprecisely

estimated variance, which could impact on the design of a future definitive study (Julious, 2005). With considering these factors, recommendations by Lancaster et al. (2004) on sample size estimation in feasibility study were considered. According to their justification, a general rule of thumb is to take 30 patients or greater to estimate a parameter. It was estimated to recruit a sample of 100 CR patients in this study.

Control

The control group received usual care. They were not exposed to the study intervention. All participants were offered the standard outpatient CR programme provided by hospitals, which involved education classes and supervised exercise (See Section 1.2.1).

Definition of Usual Care

For the purposes of this study, usual care was defined as the CR care that was currently provided for CHD patients 4 to 6 weeks after discharge from hospitals in Iran which involved supervised and structured exercise training in combination with educational and psychological support and advice on risk factors.

According to the Iranian CR protocol obtained from the study setting, all patients complete the 24 sessions in an average of 8 weeks. The first session of outpatient CR programme involves a baseline assessment by a physician and delivering information on various topics including cardio-protective medications in a group setting, presenting by a physician both verbally and in written form. Each exercise session consists of endurance training on a cycle ergo-meter for 10 to 12 minutes, an arm ergo-meter for 8 to 10 minutes and treadmills for 10 to 15 minutes. Each step includes warm up, training at constant workload, cool down, and post exercise recovery (Moghadam et al., 2008).

In all sessions, electrocardiogram and heart rate are supervised by telemetry monitoring. At the beginning, exercise intensity is set at 40 to 55% of the individual maximum Heart Rate (HR) obtained in the patients' pre-study graded exercise test, and then will be increased progressively to reach 70 to 85% maximum HR. Progressive updating of the exercise prescription is according to the patients' HR, tolerance level and cardiac symptoms (Moghadam et al., 2008). All patients undergo a stress test and echocardiogram to assess their cardiac function capacity and ejection

fraction prior and at the end of the CR programme. No mHealth adherence intervention was provided to patients who received the usual care.

Intervention

The participants in the intervention group received mobile phone/ mHealth medication adherence intervention over the 12 weeks of the study. A detailed description of the study intervention is presented in 5.1.1. The researcher also followed up with the participants in the intervention group via telephone calls once every two weeks during the study to reassure the delivery of reminders and to enquire about any patient's emergency readmission.

Random Allocation

All participants were randomised to achieve groups that are similar in terms of socio-demographic characteristics and treatments except receiving the study intervention. A random numbers table was used to generate the random allocation sequence (based on the daily admission rate, 20 random numbers were generated for each day). Patients were asked to choose between sealed non-transparent envelopes with a number inside. Odd numbers were allocated to the intervention group and even numbers to the usual care group.

Blinding

Due to the nature of the intervention, it was impossible to blind either the participants or the researcher to the study group assignment. To prevent potential bias in the results of the study, participants' follow-up visits took place after they were visited by cardiologists and CR specialists who were unaware of the study group assignment to assess the participants' EF and FC based on treadmill test or exercise test and echocardiography reports at the end of their hospital-based CR sessions.

Data Collection

All participants were assessed by the researcher in the study site two times: at baseline (pre-test, T1) and at the endpoint of the study (post-test, after 12 weeks, T2). At each point in time, the primary and secondary outcomes were measured. The primary outcome of interest was the proportion of participants adhering to a

complete cardiac medication regimen at 12 weeks measured using the Morisky Self-Reported Medication Adherence Scale (Morisky and DiMatteo, 2011, Morisky et al., 2008) (see Appendix 6). Secondary outcomes were Medication Adherence Self-Efficacy (MASE) (see Appendix 12); Cardiac Functional Capacity (FC) (see Appendix 13); Cardiac Ejection Fraction (EF); CHD-related Readmission/Mortality Rate, Health-related Quality of Life (HR-QOL) (see Appendix 8) and patients' perception about the applied intervention (see Appendix 14). At the endpoint of the study, patients who received the mHealth medication reminder intervention were asked to complete a survey about their satisfaction with the intervention. Research data were collected using the instruments below:

1. Sociodemographic Questionnaire (see Appendix 3)

Sociodemographic data was obtained at the recruitment time. Sociodemographic factors such as age, gender, education level, marital status, employment, living arrangement, monthly income and receiving health insurance services were asked only in the pre-test questionnaire.

2. Self-Reported Medication Adherence Scale (see Appendix 6)

A complete description of the instrument has been provided in Section 5.3 under Data Collection sub-section. Two questionnaires, one pre-test, one post-test, were completed by all participants. For comparability, questions at post-test were mostly similar to those at pre-test.

3. Medication Adherence Self-Efficacy (MASE) (see Appendix 12)

Self-efficacy has been found to influence a variety of health behaviours including medication adherence in chronic conditions (Saffari et al., 2015). Self-efficacy can be assessed using relevant instruments that have been developed and used in different chronic diseases such as antiretroviral therapy (Colbert et al., 2013), inflammatory bowel disease (Izaguirre and Keefer, 2014), mental illness (Sánchez et al., 2016) and diabetes (Sleath et al., 2016). The Medication Adherence Self-Efficacy Scale (MASES) has been developed by Ogedegbe and colleagues to measure and identify the patients' concerns related to self-efficacy in adherence to prescribed medications in hypertensive African-American patients (Ogedegbe et al., 2003). The 26-item, patient-derived and self-reported MASES is a reliable, stable, and internally

consistent measure of self-efficacy with Cronbach's alpha coefficient of 0.95 (Ogedegbe et al., 2003).

As a research instrument, the MASE can contribute to provide an important outcome variable. For example, self-efficacy can be evaluated over time as an outcome of a specific intervention, and hence the tool can be applied to assess within group or between group differences in self-efficacy over the study time (Ogedegbe et al., 2003). The Persian version of the MASE was used in this study to evaluate the effect of the mHealth intervention designed based on the Bandura's Self-efficacy Theory to enhance CHD patients' medication adherence self-efficacy. The Persian version of this scale was validated and reliable with Cronbach's alpha coefficient of >0.92 (Saffari et al., 2015). Two questionnaires, one pre-test, one post-test, were completed by all participants. They were provided with a description that they need to choose their level of confidence in taking their cardio-protective medications in different situations using a three-point Likert scale (1= not at all sure, 2= somewhat sure, and 3= very sure). A summary score of all responses was calculated with greater scores illustrating higher self-efficacy. It only took 5 minutes to answer the questionnaire during their recruitment session and follow-up visits and the questions were easy to understand for the patients. Permission to use of the MASE and its Persian version were obtained from the owners (see Appendix 15).

4. Functional Capacity (FC) (see Appendix 13) and Ejection Fraction (EF)

The patient's functional classification may improve as recovery from an acute event, such as Myocardial Infarction (MI), occurs or as intervention is optimised. Conversely, it declines with worsening or non-adherence to the treatment regimen (Woods, Froelicher, & Motzer, 2000). The NYHA classification system has an adequate validity and reliability in measuring functional status, assessing symptom severity and monitoring the effects of treatment in patients with cardiac disease and correlates with other measures of function, such as maximal aerobic capacity ($VO_2\text{max}$), the Specific Activity Scale (SAS), and the 6-minute walk test (Cutrona et al., 2010, Bennett et al., 2002). The role of this measuring tool has expanded over time from classification of heart failure patients to categorise all patients experienced a cardiovascular event and correlates fairly well with prognosis (Bennett et al.,

2002). NYHA classification scheme as a clinical outcome measure of this study includes multiple criteria for assessment. These criteria are varied from vital sign changes interfere with daily activities to objective assessment recommended in the ninth edition, by the Criteria Committee of the American Heart Association, New York City Affiliate (1994), which is based on measurements such as electrocardiograms, stress tests, x-rays, echocardiograms, and radiological images. The objective assessment can address the question of subjectivity which is a common critique of this measure.

In the present study, Left Ventricular Ejection Fraction (LVEF) was considered as one of the objective secondary outcomes of the study. Acute Coronary events including Acute Myocardial Infarction (AMI) can pathologically increase Left Ventricular (LV) mass and volume (i.e. LV remodelling) characterised by functional decline or reduced LVEF that is associated with increased risk of chronic heart failure, morbidity and mortality (McGregor et al., 2015). In CHD patients, adherence to medical treatment improves functional myocardial recovery and clinical outcome and eliminates the risk of CHF (McGregor et al., 2015, Tendera et al., 2009). Patients' functional status and LVEF were recorded at the baseline and at the end-point of the study based upon the most recent patients' documents, to reduce the limitations of self-reporting.

5. Short Form Health Survey Version 2.0 (SF-12v2) (see Appendix 8)

A complete description of the instrument has been provided in Section 5.2.1 under Data Collection sub-section. Two questionnaires, one pre-test, one post-test, were completed by all participants. For comparability, questions at post-test are mostly similar to those at pre-test.

6. Other Study Measures

CHD-related readmission and mortality rate were compared at the end point of the study between the two study groups using the most recent patients' medical documents.

To evaluate the acceptability of the mHealth intervention, participants who received medication reminders were asked to complete a self-administered survey adopted from the previous study (Khonsari et al., 2015). The survey consisted of 2

multiple choice questions, 4 questions with 5-point Likert scales answers and 1 open-ended question to identify the patients' perceptions about the applied mHealth intervention. The survey design was primarily based on the principles of the Roger's Diffusion Theory that consisted of four major attributes to describe how innovations are perceived by their recipients (e.g. CHD patients) (Rogers, 2003). These attributes are: (1) simplicity (the extent to which an innovation is thought as easy/ difficult to use), (2) compatibility (the innovation consistency with the potential users' needs), (3) observability (any observable effect of an innovation over time) and (4) relative advantage of an innovation that may have an impact on the rate of innovation adoption by users. It took less than 5 minutes for patients to answer the survey questions (Appendix 14).

Variables

The study instruments measured the key variables. The independent and dependent variables for investigation in this study are presented in Section 4.4.

Data Analysis

The data analysis is intended to provide the answer to the research question. Thus, it must be planned ahead along with the rest of the study (Polit and Beck, 2004). All data were analysed using the computer program Statistical Packages for Social Sciences (SPSS) version 21. The significance level in this study is $\alpha=0.05$. Both descriptive and inferential analysis were carried out using SPSS.

Quantitative/ statistical analysis, in this pilot RCT, comprised of sufficient data screening methods to identify miscoded and missing data, descriptive and inferential analysis. After coding, processing and cleaning the raw data obtained during the data collection period, frequencies and percentages were used to present detailed information on nominal and ordinal (categorical) data (such as gender, marital status, educational level, employment status, mobile phone ownership). Mean and Standard Deviation (SD) were used to describe continuous variables such as age, length of hospital stay, and number of daily medications.

Inferential statistical analysis was applied in order to evaluate the effectiveness of the mHealth intervention. In order to measure the strength of association between

two variables, a correlational procedure was performed (e.g. self-efficacy and medication adherence).

The normality of the distribution of scores related to primary and secondary outcomes was assessed using the Kolmogorov-Smirnov test. Patients' characteristics are compared between the study groups (control and intervention) using independent samples t-tests for continuous variables or χ^2 tests for categorical variables. The primary outcome from the MMAS provided categorical data including high adherence (score of 8), medium adherence (score of 6 to <8) and low adherence (scores of <6).

All secondary outcomes results were provided in categorical data including patient's cardiac FC (Class I: no symptoms, II: mild symptoms, III: marked limitation and IV: severe limitations), as well as death and hospital readmission rates except the scores of perceived MASE, EF, and HR-QOL. The chi-square (χ^2) test was applied for MMAS, cardiac FC and death/ hospital readmission rates in order to determine the statistical significance of the observed association in a cross-tabulation. One of the assumptions underlying the use of chi-square is to ensure the cell sample size is adequate. Cases where more than 20% of the cells had an expected frequency of less than five subjects were reduced by grouping patients into smaller numbers of categories (Pallant and Manual, 2007). Cells with no frequencies were treated similarly. The Cramer's Phi (ϕ) or V and the Relative Risk (RR) were reported as magnitude of the intervention effect.

In order to determine any significant changes in primary and secondary outcomes in each group over the study period, a Mann-Whitney U test (for continuous data) or Wilcoxon signed-rank test (for categorical data) was performed. The Multiple Logistic Regression was used to assess any association between socio-demographic variables and medication adherence.

To calculate the PCS-12 and the MCS-12 from the scores of perceived quality of life, the QualityMetric Health Outcomes Scoring Software 2 was used. The software uses all the 12 items of SF12V2 to produce scores for the PCS-12 and the MCS-12 and applies a norm-based scoring algorithm empirically derived from the data of a United States (US) general population survey (Saris-Baglana et al., 2007).

In theory the possible scores for the PCS-12 and the MCS-12 could be ranged from 0 (the worst) to 100 (the best). The t-test was used for comparison.

5.4 Ethical Considerations

To develop a sound knowledge and understanding of the ethical principles underpinning research is the responsibility of researchers. Such knowledge and understanding facilitates the design of ethically acceptable research (Bradbury-Jones and Alcock, 2010). The Nuremberg Code and the World Medical Association Declaration of Helsinki provided general ethical guidelines for research involving human subjects, adopted in 1964 mainly from the history of abuses of human research subjects and then later revised (seventh version), most recently in 2013 (Muthuswamy, 2014, Ndebele, 2013). By changing the format and including several subsections, the revised declaration enhances and improves clarity regarding specific issues. By so doing, the Declaration of Helsinki is a better and more important authority at what it is aimed at achieving, providing guidance on conducting medical research involving humans (Ndebele, 2013).

Most disciplines including nursing have established their own code of ethics and there is considerable overlap in the basic principles articulated in these documents such as requirements of guaranteed anonymity and/or confidentiality, informed consent, maintenance of dignity and an overall benefit to the individual/society rather than harm (Polit and Beck, 2004).

For both types of research (i.e. quantitative and qualitative methods), the Economic and Social Research Council (ESRC) (2015), the UK's principal body for funding social science research, suggested six key principles of ethical research that are presented in Table 5.3 along with the steps undertaken to address potential ethical issues.

Table 5.3. Key principles of ethical research (ESRC, 2015, p.4) and steps undertaken to address ethical concerns

Key principles of ethical research	Steps undertaken to address ethical concerns
1 Research participants should take part voluntarily, free from any coercion or undue influence, and their rights, dignity and (when possible) autonomy should be respected and appropriately protected.	<ul style="list-style-type: none"> • Obtained ethics approval from the School of Health in Social Science Ethics Committee at the University of Edinburgh and the Institutional Review Board of the University in Tehran.
2 Research should be worthwhile and provide value that outweighs any risk or harm. Researchers should aim to maximise the benefit of the research and minimise potential risk of harm to participants and researchers. All potential risk and harm should be mitigated by robust precautions.	<ul style="list-style-type: none"> • All participants were fully informed about this research, such as its purpose and process both verbally and written by providing participants' information sheets. • Participants were assured of the anonymity of their participation. • Their participation in this research was requested in a relaxed atmosphere.
3 Research staff and participants should be given appropriate information about the purpose, methods and intended uses of the research, what their participation in the research entails and what risks and benefits, if any, are involved.	<ul style="list-style-type: none"> • During all phases of this research, any potential harm or risk could be inflicted upon the participants were reviewed, and the participants were frequently asked about their feelings regarding participation in this research.
4 Individual research participant and group preferences regarding anonymity should be respected and participant requirements concerning the confidential nature of information and personal data should be respected.	<ul style="list-style-type: none"> • This research was independent from sponsors or funders, and no conflicts of interest were encountered during the course of this research.
5 Research should be designed, reviewed and undertaken to ensure recognised standards of integrity are met, and quality and transparency are assured.	<ul style="list-style-type: none"> • In case of any unpredicted ethical issue, a plan was established to contact the PhD principal supervisor and the School of Health in Social Science Ethics Committee at the University of Edinburgh and Tehran University of Medical Science in order to respond immediately and actively to ethical issues, should they emerge. However, no ethical issue emerged in the duration of this research.
6 The independence of research should be clear, and any conflicts of interest or partiality should be explicit.	

One of the most fundamental ethical principles in research is that of beneficence that contains multiple dimensions and follows the principle of doing good in terms of that which would help, improve and benefit the individual (Polit and Beck, 2004). The results of this research increased existing knowledge and understanding within this area in the Iranian context. This knowledge will be disseminated internationally in order to help shape clinical practice in the future. Although this research may benefit future patients, it is also important to consider the effects on those patients participated in the research study.

Minimising all types of harm and discomfort and achieving a balance between the potential benefits and risks of being a participant should be considered by researchers as an important dimension of beneficence (Polit and Beck, 2004). An exclusion criterion was created for the study in order to protect those patients deemed vulnerable/inappropriate for the experiment. The researcher is a nurse whose clinical judgement was used during recruitment to exclude those who were ill and might have been harmed, and during the administration of interventions.

According to the principle concerning justice, participants have the right of fair treatment and privacy before, during, and after their participation in the study (Polit and Beck, 2004). In this study, the experimental intervention however, was an addition to the usual care which cardiac patients received after discharge from a hospital. Thus, no treatment was withheld from patients which they should have been entitled to during their period of care. At the end of the quantitative pilot RCT, a text message was sent to all participants in the intervention group in order to convey the appreciation of their participation in the study and inform them that no more medication reminder would be sent to their mobile phones, but that they still needed to continue their medication taking according to their prescriptions. Additional information were also provided for all participants so that they could contact CR staff with any further questions or concerns related to their medications.

Confidentiality of participants in both qualitative and quantitative research were maintained. Data was managed in accordance with the University of Edinburgh guidelines. The confidentiality of all data that was collected, processed and stored for the purposes of the study was maintained in compliance with Good Clinical Practice (GCP) guidelines and the principles of Data Protection Act 1998. Participants were assigned a unique study number on all digital and typed forms of data to ensure anonymity. A file of study numbers linked to participants identifying information were stored separate from other data, including consent forms. All written data were kept in a locked filing cabinet and all computer data were password protected. It was also agreed with the text message service provider that patients' mobile phone numbers would not be sold or passed on to a third party in any case without explicit consent (see Appendix 16)

5.4.1 Ethical Approval

Ethical approval obtained from The School of Health in Social Science, The University of Edinburgh Research Ethics Committee (Ethics Approval Code: NURS006) (see Appendix 17) and the Institutional Review Board of the University in Tehran (Ethics Approval Code: 92-04-28-28802-145738) (see Appendix 18). Study was carried out in accordance to the principles outlined in the Declaration of Helsinki. The anonymity of every patient was guaranteed because all data were coded. Written informed consent were obtained from each participant.

5.4.2 Consent Form

Respect for human dignity is an ethical principle that includes the right to self-determination (i.e. participants' right to decide voluntarily whether to participate, without treatment alteration) and the right to full disclosure (i.e. providing a full description about the nature of the study, the right to refuse participation, the researcher's responsibilities, and likely risks and benefits) (Polit and Beck, 2004). Participants' information sheets (Appendix 19) were developed for the purpose of each study phases. These information sheets guaranteed participants' confidentiality, provided them with a description of the study, the reason for the study and what would be involved if they agreed to participate. The participants' information sheets received approval from the Institutional Research Ethics Committee in Edinburgh and Tehran. Patients' consent was obtained after allowing enough time (range: 10-15 minutes) to participants to read the information sheet and both participant and researcher agreed together that the participant had all the relevant information to make an informed choice regarding their decision to participate. The consent forms (Appendix 20) used had been provided according to the template accessed via Institutional Research Ethics Committee, highlighting the participant's right to refuse without compromising his/her clinical treatment and again highlighted the assurance of confidentiality.

5.5 Negotiating Access

Since this study took place outside the UK (place of education), it was decided to secure an external support that would strengthen access negotiations by choosing a local supervisor - Professor (ARN) - based in the Tehran University of Medical

Science in Iran. In April 2015, a teleconference was arranged to connect PhD supervisors in the University of Edinburgh with Prof. ARN so that they could discuss the research project and how the researcher could gain access to potential study sites. Following the discussion, the researcher travelled to Tehran for obtaining Ethical Approval, identification of potential study setting and initial negotiations with gatekeepers in May 2015. Ethical Approval (Ethics Approval Code: 92-04-28-28802-145738) (see Appendix 18) as well as a letter of permission (see Appendix 21) obtained from the Tehran University of Medical Sciences. A letter of ethics approval was also obtained from the hospital in which the pilot RCT was conducted (see Appendix 22). Following receipt of permissions, the researcher (SKh) met with CR clinic manager, Principal Nurse Supervisors/ Matrons of three hospitals (two cardiovascular, medical and research centres and one tertiary hospital covering a large mixed urban and rural area with a diversity of social groupings) affiliated to Tehran University of Medical Sciences and the Director of Iranian Cardiac Nurses' Association involved with permission for access requested. These meetings had been arranged by Prof. ARN in Tehran University of Medical Sciences in advance. During the meetings, SKh introduced herself, explained about the research proposal, and identified needs, expectations and potential benefits from this particular collaboration. This allowed the researcher to familiarise herself with hospital regulations and discussions with experts regarding the conduct of the study to take place. There were no similar programme to the mHealth medication adherence intervention employed by those hospitals for cardiovascular patients. This was important in order to control for the effects of potential sample contamination caused by such existing programme.

5.6 Visual Model of the Research Process and Data Collection

In this mixed methods study a visual model was used to show the research process and phases of the study, along with the data collection and follow-up procedures. Figure 5.2 in the next page presents the visual model of this mixed-methods study.

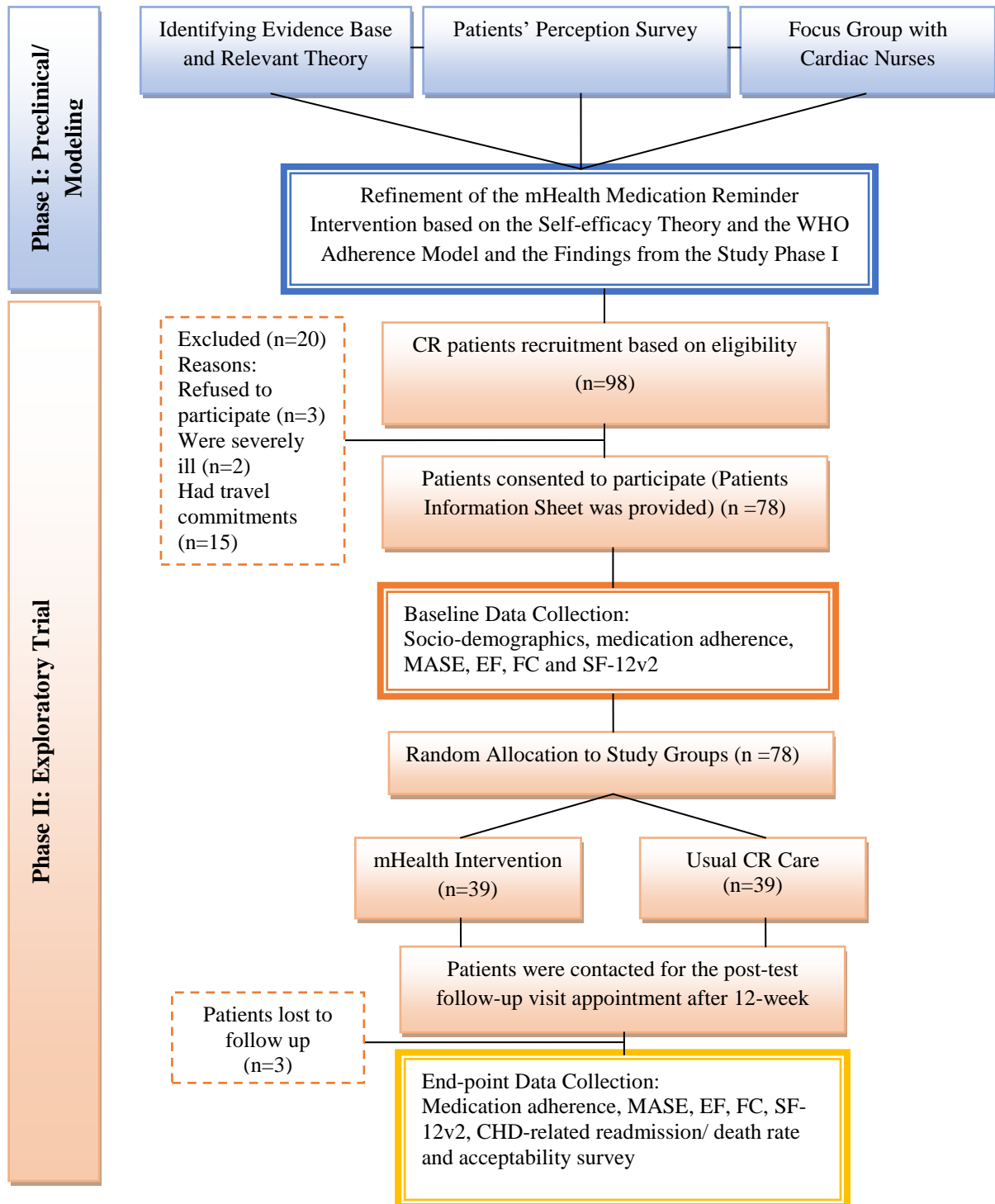


Figure 5.2. Visual model of the research process and data collection

5.7 Summary

This chapter has introduced and critiqued the rationale to select a multi-stage mixed methods research design (i.e., the patients' perception survey (quantitative), focus group discussions with cardiac nurses (qualitative) and pilot RCT (quantitative)) as a research strategy to enable the refinement and evaluation of the mHealth medication reminder intervention to promote cardio-protective medications among CHD patients in an Iranian CR setting. Particularly, the MRC framework was used as a guide to develop the preclinical/ modelling phase and the exploratory trial phase of the study.

This chapter also explained the data collection and analysis processes of each phase of this study in detail. Moreover, this mixed method research has attempted to assure the ethical considerations. A visual model of the data collection procedure was presented to visualise the research process and phases of the study as well as the data collection and follow-up procedures. In the following chapter, the findings of this research that were derived from these methodological strategies are discussed.

CHAPTER 6: RESULTS

This Chapter provides the results of the studies undertaken in Phase 1 (i.e. preclinical/ remodelling) and Phase 2 (i.e. exploratory trial) to refine and evaluate a mHealth intervention to improve medication adherence in Cardiac Rehabilitation (CR) outpatients in Iran. Firstly, the survey results are reported that identified the pattern of ownership and utilisation of mobile phones in Iranian CHD patients and their preferences about a mHealth medication adherence intervention. Next, the results of the qualitative focus groups study that explored Iranian cardiac nurses' perspectives about the potential effects, barriers and facilitators to implementation of a mHealth intervention among Iranian CHD patients are presented.

The survey and focus group findings were used to inform the second phase of the research, the pilot Randomised Controlled Trial (RCT). The results of the pilot RCT, undertaken to evaluate the effect of the study intervention on CR patients' medication adherence, are reported. The detailed aim and objectives of the study can be found in Section 4.2.

6.1 Preclinical/ Modelling (Phase 1) Results

The results of the first phase of the study as part of the preclinical/ modelling phase are presented in two sections including the results of the self-completed survey of CHD patients (Section 6.1.1) as well as the results of the cardiac nurses' focus group (Section 6.1.2) that were used to inform the second phase of the study.

6.1.1 Survey Study Results

The survey results reported here were conducted as preliminary research prior to the initiation of a pilot RCT of the mHealth intervention to enhance adherence to cardiovascular medications among CHD patients in an Iranian CR setting. Specifically, the survey sought to identify:

- The pattern of ownership and utilisation of mobile phones in Iranian CHD patients (Objective 1);
- A preferable design for the study intervention based on Iranian CHD patients' opinions (Objective 2).

Participant Characteristics

Overall, 132 Iranian CHD patients were approached from outpatient CR clinic of an educational research and medical centre for cardiovascular disease affiliated to Tehran University of Medical Sciences for participation in the survey. Of 9 patients who declined to complete the survey, 5 stated they were “not interested” and 4 said their reason for non-participation was due to “time limitation”. Of the 123 respondents recruited from the CR clinic consenting to participate, 44.7% (55/ 123) were Acute Coronary Syndrome (ACS) patients, 34.1% (42/ 123) underwent a cardiac revascularisation (stenting or bypass surgery) and 21.1% (26/ 123) suffered from heart diseases other than Coronary Artery Disease (CAD) (i.e. heart valve disease, dysrhythmia, Left/ Right Bundle Branch Blocks). The mean age was 57.24 with a Standard Deviation (SD) of ± 11.2 years, 72.4% were male, around one-third had secondary school education and almost 83% were married. Around 44% (54/ 123) of respondents were retired with self-reported ‘quite enough’ monthly income and the majority (90.2%) had health insurance. 88.6% (109/ 123) were living with their family. The mean length of hospital stay was 17.57 (SD ± 13.1) days and the mean for the number of medications consumed by patients were 5.35 (SD ± 2.7) per day. Detailed participant demographic characteristics compared to a national cross-sectional and epidemiological study of cardiovascular patients registered in Iran Health and Medical Education Ministry (Department of Cardiovascular Disease Prevention) (Ahmadi et al., 2015) are presented in Table 6.1.

Ownership and Utilisation of Mobile Phones (Objective 1)

The majority of respondents (98.4% or 121/ 123) owned mobile phones and around 96% (118/ 123) kept the phone in their own possession. A total of 42.3% (52/ 123) had a Smartphone. Participants had owned a mobile phone for a mean of 10.87 (SD ± 5.8) years. OF 123 respondents, 68.3% used the Short Message Service (SMS) technology to send/ receive text messages to and from their mobile phones. Education was significantly associated with the usage of SMS, Odds Ratio (OR) =4.40 with 95% Confidence Interval (CI) of 1.86-10.4, $P < 0.001$.

Slightly over half of the participants knew how to connect their phones to the Internet. However, only one-third used their phones to connect to the Internet.

Similar to the usage of SMS, education was significantly associated with the utilisation of the Internet on mobile phones, OR=7.16 (95% CI: 2.3-22.26), P<0.001.

In this study, 53.7% (66/123) of the patients used alarm function on their phone devices. Only 5.7% (7/123) set the alarm specifically as a medication reminder alone.

Table 6.1. Characteristics of survey participants

Characteristics	Overall	Population ^b
Age, mean (\pm SD), years	57.24 (\pm 11.2)	61.2 (\pm 13.4)
Male	59.05 (\pm 10.9)	59.6 (\pm 13.3)
Female	52.52 (\pm 10.7)	65.4 (\pm 12.6)
Sex		
Male	89 (72.4)	15,033 (72.45)
Female	34 (27.6)	5,717 (27.55)
Education		
Primary or less		
Male	28 (31.5)	5488 (36.5)
Female	12 (35.3)	4123 (72.12)
Secondary		
Male	29 (32.6)	8332 (47.3)
Female	13 (38.2)	1541 (26.9)
University		
Male	32 (36.0)	1213 (8.1)
Female	8 (23.5)	53 (0.93)
No Answer	1 (0.8)	
Marital Status		No comparable data
Married	102 (82.9)	
Single	20 (16.3)	
No Answer	1 (0.8)	
Employment		No comparable data
Employed	36 (29.3)	
Unemployed/ Housewife	30 (24.4)	
Retired	54 (43.9)	
No Answer	3 (2.4)	
Living Arrangement		No comparable data
With family	109 (88.6)	
With relatives	9 (7.3)	
Alone	2 (1.6)	
No Answer	3 (2.4)	
Monthly Income		No comparable data
Enough	31 (25.2)	
Quite Enough	54 (43.9)	
Not Enough	29 (23.6)	
No Answer	9 (7.3)	

Characteristics	Overall	Population ^b
Insurance		No comparable data
Yes	111 (90.2)	
No	6 (4.9)	
No Answer	6 (4.9)	
Hospital Stay, mean (\pm SD), days	17.57 (\pm 13.1)	
Male	18.22 (\pm 14.6)	6.56 (\pm 14.6)
Female	15.96 (\pm 8.4)	6.53 (\pm 14.5)
Diagnosis		
ACS [*]	55 (44.7)	17958 (86.5)
CABG ^ψ	40 (32.5)	237 (1.14)
PCI [†]	2 (1.6)	1431 (6.8)
Others [‡]	26 (21.1)	1124 (5.41)
Daily Medications, mean (\pm SD)	5.35 (\pm 2.7)	No comparable data
<5	67 (54.4)	
5-9	46 (37.4)	
\geq 10	10(8.1)	

a. Data are presented as frequency (percentage) unless otherwise specified.

b. Data from a national cross-sectional and epidemiological study of cardiovascular patients registered in Iran Health and Medical Education Ministry (Department of Cardiovascular Disease Prevention).

* In this study, Acute Coronary Syndrome (ACS) refers to Unstable Angina (UA), Non-ST-segment Elevation Myocardial Infarction (NSTEMI), and ST-segment Elevation Myocardial Infarction (STEMI).

ψ CABG = Coronary Artery Bypass Grafting

† PCI = Percutaneous Coronary Intervention

‡ In this study, any cardiovascular problem other than ACS, CABG and PCI considered as “other diagnosis” including heart valve disease, dysrhythmia, Left/ Right Bundle Branch Blocks.

Patients’ Perceptions about mHealth Intervention (Objective 2)

Almost 93% of participants perceived that receiving automatic reminders on their mobile phones would help them to remember to take their medications. Participants (48%) stated they would prefer to receive medication reminders via SMS on their mobile phones. Based on patients’ responses, the most preferred frequencies to receive medication reminders were “as often as the medications need to be taken” (50.4 %) and “on a daily basis” (28.5%), respectively.

In terms of SMS timing, 44.7% stated they would like reminders to be sent just before the medication time, following 16.3% specified mornings (6 am–10 am) as the best time to receive SMS medication reminders.

With regards to SMS reminder contents, patients were asked to write a short statement as an example of their preferred text message reminder. Of 123 respondents, 55.3% did not have any preference.

The most popular examples were as follow:

“It is time to take your medications” (13%)

“Don't forget to take your medications” (11.4%)

Participants (74%) did not perceive mobile phone-based medication reminders as an intrusion in a person’s life and 72.3% reported an interest in receiving a text message intervention for their cardiac medications. Almost 45% of respondents stated they would prefer not to send a reply message to each reminder for the medications they would take (see Table 6.2).

Table 6.2. Ownership and Utilisation of Mobile Phones in Survey Participants (n=123)

No.	Survey Questions	Overall (%) ^a
1	Do you have a mobile phone?	
	Yes	121 (98.4)
	No (Have no use for it)	1(0.8)
	No (Inability to use)	1(0.8)
2	Is this phone mostly kept in your possession?	
	Yes	118 (95.9)
	No	1 (0.8)
	No Answer	4 (3.3)
3	Since when have you used mobile phones?	
	Mean (\pm SD), years	10.87 (\pm 5.8)
4	Do you use the SMS function on your mobile phones?	
	Yes	84 (68.3)
	No	34 (27.6)
	No Answer	5 (4.1)
5	Can you connect to the Internet with your mobile phone?	
	Yes	62 (50.4)
	No	47 (38.2)
	Don't Know	8 (6.5)
	No Answer	6 (4.9)
6	Do you usually connect to the Internet with your mobile phone?	
	Yes	72 (58.5)
	No	10 (8.1)
	No Answer	
7	For a cardiac patient, would it be helpful to have automatic reminders on the mobile phone to help remind the patient to take medicines?	
	Yes	114 (92.7)
	No	7 (5.7)
	No Answer	2 (1.6)

No.	Survey Questions	Overall (%) ^a
8	Do you use the alarm function?	
	Yes	66 (53.7)
	No	50 (40.7)
	No Answer	7 (5.7)
9	What do you use the alarm function for?	
	No need to answer	50 (40.7)
	a. To wake up	35 (28.5)
	b. To remind me of errands	6 (4.9)
	c. As a reminder for medicines	7 (5.7)
	d. Both a & b	4 (3.3)
	e. Both a & c	7 (5.7)
	f. All Above	6 (4.9)
	No Answer	8 (6.5)
10	What other use do you have for the mobile phones?	
	a. Listen to radio	3 (2.4)
	b. Play games	5 (4.1)
	c. Camera	11 (8.9)
	d. a & c	1 (0.8)
	e. Other	28 (22.8)
	f. None	71 (57.7)
	No Answer	4 (3.3)
11	If we were to provide automatic reminders to patients to take medications, what format would you like these reminders to be in?	
	Telephone call	28 (22.8)
	SMS message	59 (48.0)
	Smartphone application	6 (4.9)
	No preference	24 (19.5)
	No Answer	6 (4.9)
12	How often would you like these medication reminders to be sent to the patient?	
	As often as the medications need to be taken	62 (50.4)
	Daily	35 (28.5)
	Once a week	11 (8.9)
	Twice a week	3 (2.4)
	No Answer	12 (9.8)
13	What times would you like the reminders to be sent to you?	
	Just before the drugs timings	55 (44.7)
	Morning: 6 am – 10 am	20 (16.3)
	Mid-day: 11 am – 2 pm	8 (6.5)
	Evening: 3 pm – 6 pm	6 (4.9)
	Late evening/night: 7 pm – 10 pm	7 (5.7)
	Anytime	21 (17.1)
	No Answer	6 (4.9)
14	Do you have a Smartphone?	
	Yes	52 (42.3)
	No	51 (41.5)
	Don't Know	13 (10.6)
	No Answer	7 (5.7)

No.	Survey Questions	Overall (%) ^a
15	Do you use Smartphone applications?	
	Yes	37 (30.1)
	No	73 (59.3)
	No Answer	13 (10.6)
16	If we were going to develop an application using cell phones for cardiac patients – what other possibilities do you think would be useful?	
	a. Communication with health provider	52 (42.3)
	b. Information on medicines	20 (16.3)
	c. Motivational Messages	15 (12.2)
	d. a & b	8 (6.5)
	e. a & c	3 (2.4)
	f. All Above	6 (4.9)
	No Answer	19 (15.4)
17	Do you prefer to send a reply message to each reminder when you take your medication?	
	Yes	42 (34.1)
	No	55 (44.7)
	Don't Know	17 (13.8)
	No Answer	9 (7.3)
18	Do you think the cell phone used in this way will be an intrusion into a person's life?	
	Yes	14 (11.4)
	No	91 (74.0)
	Don't Know	12 (9.8)
	No Answer	6 (4.9)
19	Would you like to enrol you as a participant in receiving medication reminders?	
	Yes	90 (73.2)
	No	30 (24.4)
	No Answer	3 (2.4)

a. Data are presented as frequency (percentage) unless otherwise specified.

6.1.2 Qualitative Focus Groups Results

Three Focus Groups Discussions (FGDs) were conducted among 23 Iranian cardiac nurses to inform the refinement of the study mHealth intervention to promote cardiac medication adherence among CHD patients at risk of non-adherence. FGDs specific objectives were to explore:

- Nurses' perspectives of the potential effect of a mHealth intervention among Iranian CHD patients (Objective 3);
- Barriers and facilitators to implementation of the mHealth intervention through which such interventions may affect medication adherence in an Iranian context (Objective 4).

The analysis of the focus group data identified three key themes:

1. Positive impacts;
2. Unpreparedness for mHealth implementation; and
3. Considerations before implementation.

Participant characteristics and identified themes are presented separately below.

Participant Characteristics

The mean age of nurse participants was 36.64 (SD±6.69) years, predominantly female (82.6%), married (60.9%), with an average of 12.06 (SD±6.51) years work experience. Table 6.3 and 6.4 presents the characteristics of FGDs' participants.

Table 6.3. Characteristics of focus groups participants (n=23)

Characteristics	Overall (%)
Age, mean (\pm SD), years	36.64 (\pm 6.69)
Sex	
Male	4 (17.4)
Female	19 (82.6)
Education	
Bachelor's	19 (82.6)
Master or Higher	4 (17.4)
Marital Status	
Married	14 (60.9)
Single	9 (39.1)
Hospital Ward	
Cardiac Rehabilitation	7 (30.4)
Cardiac Intensive Care	9 (39.1)
Hospital Nursing Department	3 (13.0)
Other Cardiology Wards	4 (17.4)
Position	
Staff Nurse	17 (73.9)
Head Nurse (Nursing Unit Manager)	2 (8.7)
Supervisor	3 (13.0)
Ward Administrator	1 (4.3)
Working Experience, mean (\pm SD), years	12.06 (\pm 6.51)
Working Experience, years	
<5	3 (13.0)
5-9	4 (17.4)
10-14	8 (34.8)
15-19	6 (26.1)
\geq 20	2 (8.7)
Have you ever participated in any mHealth Seminars?	
Yes	3 (13.0)
No	20 (87.0)

Table 6.4. Detailed characteristics of focus groups participants (n=23)

No.	Sex ^a	Age (Years)	Education ^b	Marital ^c	Hospital Ward ^d	Work Experience (Years)	Any mHealth Seminars?
1	F	40	BSN	S	CICU	13	Yes
2	F	54	BSN	M	Others	29	No
3	M	27	MSc or Higher	S	CICU	6	No
4	F	34	MSc or Higher	M	CICU	8	Yes
5	F	24	BSN	M	CICU	<1	No
6	F	33	BSN	S	CICU	12	No
7	M	34	MSc or Higher	M	HND	10	Yes
8	F	37	BSN	S	Others	15	No
9	F	46	BSN	S	HND	21	No
10	F	37	BSN	M	CICU	5	No
11	F	40	BSN	M	CICU	14	No
12	M	37	MSc or Higher	M	HND	15	No
13	F	35	BSN	S	CICU	10	No
14	F	37	BSN	S	CICU	13	No
15	F	30	BSN	S	Others	2.5	No
16	F	24	BSN	S	Others	2	No
17	M	42	BSN	M	CR	17	No
18	F	40	BSN	M	CR	17.5	No
19	F	35	BSN	M	CR	8	No
20	F	36	BSN	M	CR	14	No
21	F	39	BSN	M	CR	14	No
22	F	42	BSN	M	CR	15	No
23	F	40	BSN	M	CR	16	No

a. F=Female, M=Male;

b. BSN=Bachelor of Science in Nursing, MSc=Master of Science in Nursing;

c. S=Single, M=Married;

Positive Impacts

Participants in all FGDs perceived mobile phone-based interventions as being beneficial to cardiac patients and their medication taking. Within the theme of ‘Positive Impacts’, three sub-themes are presented; the nurses identified that mHealth-based interventions would act as a reminder, connect hospital to home and prevent negative outcomes of medication mismanagement.

Acting as a reminder

Cardiac nurses participating in FGDs felt that the intervention would be most helpful to those patients who tend to forget or who are so busy and preoccupied with other priorities that taking medications might be ignored. An illustrative quote included:

“I think these kinds of interventions are likely to be beneficial because it will remind that person to take their medications. From my own experience, patients simply forget to take their medications; it is common not only among cardiac patients but among the majority of patients in their busy lives” (Participant 1, FG 1).

“It can really work especially for those patients who are forgetful. Some of them are so busy; but this intervention sends them reminders so that they’ll remember...now, it’s time for taking medications” (Participant 10, FG 2).

“When you send reminders for their medications, they will never forget and it is a plus; some patients need to be reminded to take their pills. So the intervention you are trying to develop is what they really need!” (Participant 21, FG 3).

Across all the focus group interviews, the nurses stated that the first months of hospital discharge are high risk for cardiac patients to forget the name, dose and instructions for their prescribed medications. One of the nurses expressed:

“The most high risk time is when patients discharge from the hospital. I mean...when they are at home and they may forget when and how to take their drugs” (Participant 11, FG 2).

“When patients are in hospital, nurses are responsible to administer their medications and so they do not have any concern about their medications; problem will occur when they are no longer at hospital. It is difficult for them to remember their newly prescribed medications and they may return to the hospital during the first months after discharge with many difficulties” (Participant 20, FG 3).

Almost all of the staff nurses in the FGDs believed that the risk of non-adherence may reduce as they received medication text message reminders. They discussed patients’ forgetfulness in early hospital post-discharge being due to the negative mental consequences of cardiovascular diseases and that sending text messages for reminding them about their medications could help address this problem. One of the nurses stated:

“You know problems caused by cardiac diseases are not just related to heart and coronary arteries...I read an article that there is a link between heart disease and depression and cognitive problems. Sending text message reminders to patients’

mobile phones could make it easier for patients to remember complicated prescribed medication regimen following hospital discharge” (Participant 2, FG 1).

“If some patients neglect to take their medications properly, it can be related to negative outcomes of myocardial infarction. I think it is because this event may lead to a temporary lack of oxygen to the brain. I noticed it first when one of the patients was discussing this problem with Dr. S and that's why I think they'll need text message medication reminders” (Participant 13, FG 2).

It is evident from nurses' discussions that cardiac patients may benefit from receiving the mHealth intervention for their medications since the intervention has the potential to act as a reminder. They highlighted that text-message reminders can help cardiac patients who are at risk of medication non-adherence mostly due to unintentional reasons (e.g. forgetfulness and carelessness) during the early phase of discharge from hospital.

Connecting hospital to home

The application of mHealth intervention needs to be facilitated by maintaining patient-provider communication after sending patients home. Post-discharge follow-up and interaction between patients and healthcare providers play an important role in the statements expressed by all the FG groups; for example, one of the more experienced nurses identified that there is no interaction and follow-up with patients after hospital discharge:

“Unfortunately, most of our patients are missed after going home and are no longer in contact with us. That is because our hospitals are inefficient regarding patients' post-discharge follow-up and I can say this kind of intervention is absolutely one of the essentials” (Participant 3, FG 1).

This demonstrates some of the participants figured out that there is a lack of electronic health system to provide a connection between hospital and home. They also believed that there is a limitation in providing patients with post-discharge follow-up and reminding them of their healthcare needs and treatment regimen. The example below demonstrates patient-provider connection after inpatient stay can be established through electronic follow-up using mHealth interventions.

“There is no interconnected electronic health system or mHealth in our hospitals. How we can provide follow-up for our discharged patients? You know...just a few of them may call me if they have questions about their health care

needs and medications. We are not in contact with all of patients after hospital discharge” (Participant 9, FG 2).

Nurses also appear to believe that sending medication reminders using mobile phones would make patients feel they can still be in contact with their healthcare providers and they are cared for even away from the hospital, at their home. This, in turn, would result to persuade patients to more adhere to their treatment. Viewing the intervention of text message reminders as a solution to medication non-adherence, demonstrates the nurses’ acceptance about the role of mHealth intervention to provide an ongoing connection with patients even when they are at home. This may also suggest that these participants appreciate the potential psychological impacts of post-discharge follow-up delivered by innovative interventions. Participant 18 in FG 3 said:

“Well...psychologically, patients really need this kind of intervention as a means of follow-up and support from their healthcare providers. You know, most of our cardiac patients are elderly people and live alone, they feel like yes! Someone cares about me, values me...so, it motivates him to follow his treatment”.

Within the subtheme of “connecting hospital to home”, there was some evidence that highlighted participants were aware of the importance of post-discharge patient-provider interaction to improve medication adherence and health outcomes. However, they criticised the inefficiency of healthcare organisations in Iran in providing an interconnected follow-up system. They also discussed the effect of the implementation of mHealth on preventing consequences of medication non-adherence, this leads on to the next subtheme evident in the analysis.

Preventing negative outcomes

Participants in all focus groups discussed reduction in patients’ readmissions and healthcare expenditure as another advantage of applying mobile health interventions to improve medication adherence. They believed that patients who do not follow their medication regimen would experience negative consequences. Serious complications such as rehospitalisation, prolonged inpatient stay and even death were understood to be the results of non-adherence to medication regimen that can be prevented by implementation of mHealth intervention. There was some evidence that the nurse participants associated reduction in the number of emergency

department visits and healthcare costs with improved medication taking as potential effect of the text message reminder intervention. Participant 4 in FG 1 explained this through a real example:

“Sending medication reminders are 100% beneficial...Take patients taking Warfarin for example; I saw many patients readmitted due to major hemorrhagic events and/ or toxicity from an overdose of Warfarin. Many other cardiac conditions are quite similar...I had patients that developed serious heart failure and lower extremities oedema because they forgot or were careless to take their prescribed drugs properly...”

Participant 12 in FG 2 added:

“Do you know how much money is wasted on medicines?...applying this intervention may reduce readmissions, the length of hospital stay, and even death related to nonadherence to medications...”

It would appear that the nurses showed insight into the current challenges with poor medication adherence and the implications of this for the patient themselves and also for the cost to the health system. There was even a sense of positivity in the nurses towards the application of the mHealth intervention as they believed that the text message reminders may prevent medication non-adherence and consequently may reduce the negative outcomes associated with poor medication-taking.

Unpreparedness for mHealth Implementation

Under the previous category of “positive impacts”, the nurses highlighted the issue of healthcare system inefficiency in Iran in providing a uniform electronic health system. This issue clouds the participants' perceptions about the implementation of mHealth to improve medication adherence and that is of “unpreparedness to implement mHealth” in the Iranian setting. This notion of unpreparedness for mHealth implementation forms the second theme evident in the data. Three subthemes were identified from FGs describing the reasons for being unprepared to implement mHealth in Iran including lack of Information Technology (IT) knowledge among patients and healthcare providers, legal ambiguity and healthcare system-related barriers.

Lack of IT Knowledge

The evidence presented here would suggest that in Iran there is limited education and training related to IT skills to general public and in medical education in universities and related informatics subjects. The importance of this issue is easily demonstrated by posing a question that whether everyone has adequate literacy to use text message reminders. A typical statement conveyed by participant 9 in FG 2:

“I guess sending text-message reminders may benefit a limited number of patients; I mean patients' literacy level need to be considered as part of the intervention preparation...is everyone literate to read text messages?”

This quotation shows the concern that the nurse participants expressed about cardiac patients without required literacy who may not benefit from the intervention. Participant 16 in FG 3 added:

“If there is a possibility that some patients who receive the reminders may have problems in opening and reading text messages on their mobile phones and they may not feel comfortable asking for assistance from others, they may not benefit from the intervention”.

The lack of nurse informatics speciality and basic IT knowledge among nurses and other healthcare professionals were identified as being problematic. The participants often cited cultural resistance and lack of IT skills training and practice among clinicians in hospitals and healthcare organisations as barriers to set electronic health among the major priorities in Iran. From the data it was seen that such issues were identified as evidence of the healthcare system unpreparedness to use innovative mHealth interventions for patients. It is interesting, however, that the nurses were aware that receiving IT training as part of the undergraduate programme or in-service training and continuous education are among the basic necessities for applying mHealth in health care. In the words of participant 1 in FG 1:

“Frankly speaking, we as healthcare professionals in a medical team do not have the knowledge of using assistive technology devices...I do not think that there is any related informatics course in our undergraduate programme. There is cultural resistance to change, as well...we are not ready yet...”

Participant 12 in FG2 added:

“I think if mobile health is going to happen, a proper continuous training should be performed and nurses who can work with this system should have the speciality”.

Participant 23 in FG 3 stated:

“As far as I am aware, at least in this hospital, there is no health informatics professional; I guess nursing informatics has not been introduced as a postgraduate speciality in nursing studies, yet. I myself did not receive adequate IT training as part of the Bachelor's degree programme”.

Similarly, Participant 6 in FG1 described:

“You know what?...Healthcare professionals are resistance to any change in the system that requires them to receive training for that. I think we really need a comprehensive in-service training to improve our IT knowledge and to be able to use mHealth in our country”.

It would seem that the nurse participants in this study showed an awareness that lack of IT knowledge and skills among both patients and healthcare providers may be a challenge and this may result in an obstacle to the implementation of mHealth interventions in healthcare organisations in Iran.

Legal ambiguity

The application of mHealth interventions needs to be in accordance with established legal frameworks and good practice, and requires ethical considerations. Professional boundaries and liability are crucial considerations in the use of mHealth medication reminders described by all groups; for example, participant 10 in FG 2 expressed his concerns about legal limitations of using mobile phone interventions and patients' confidentiality that may increase the risk of unethical use and illegal practices:

“I am thinking about legal limitations...sending medication reminders to patients' mobile phones...have you thought about patients' confidentiality?... some patients are not comfortable to talk with their family or friends about their heart disease...somebody may come and pick their mobile phone who does not know about their condition and he may see the text message accidentally... so this may be problematic for the patients and their families even for us as a healthcare staff from the legal aspect”.

There was some evidence that there is limited guidance in the National Code of Ethics for Nurses specifically about their responsibilities on medication administration as well as electronic health implementation in practice. This highlights the role of the national code of practice and legal framework to support nurses and address their ethical concerns. The statements from the participants in this study may suggest that ambiguous legal framework, confidentiality, data protection and security issues are evidence of unpreparedness to implement mHealth interventions in the Iranian settings that need prior considerations beforehand. The example below demonstrates the nurses' concerns about the issues related to the patients' data protection (i.e. patients' mobile phone numbers may be sold to different businesses if they are not protected against third-party telemarketers):

“How will you send the reminders?... If you consider a company to send text messages, it will become an exposure. Most of them sell mobile phone numbers to a third party for advertising reasons”. (Participant 5, FG 1)

Moreover, the nurses appear to have developed their ideas wider than just discussing some potential issues to the use of mHealth to improve medication adherence; they showed an insight and real understanding of the bigger picture of mHealth implementation in health care. Perceiving application of mHealth as a potential nursing duty, demonstrates an awareness about the role of the regulatory and legal framework that can support nurses in effective use of the technology in practice:

“I believe one of the barriers to mobile health is the lack of a legal description and a documented framework. It has the potential to be included as a nursing duty and its implementation needs legal support.” (Participant 13, FG 2)

It seems that having a legal framework with clear rules about the use of mHealth interventions may lead to a desire in nurses to apply it since they comprehend the potential positive impacts.

Healthcare system-related barriers

The preparedness to use mHealth interventions may be influenced by factors related to healthcare systems that were identified from the nurses' discussions such as absence of a comprehensive interconnected system and electronic health information as well as resistance to change. Within this subtheme of healthcare

system-related barriers, there was some evidence that showed the absence of a shared electronic health system as well as a system to order, dispense, or track medications were identified as important infrastructural problems related to implementation of mHealth medication adherence intervention. Participant 2 noted in FG 1:

“ Excuse me, but you need to consider that unfortunately there is no shared patient information system accessible for all healthcare organisations. This may cause difficulties in monitor patients’ status, their medications, etc. Medications may be changed, dosage may be titrated particularly during the early phase of patients’ discharge. However, you won’t be aware of these changes and this may cause disaster...”

Similarly, Participant 15 in FG 2 stated:

“ Our healthcare system is fragmented ... you are not able to track our patients and update their medication changes over time. This issue may increase medical errors and unnecessary costly visits to health centres”.

This limitation had an important impact in modification and remodelling of the study intervention regarding content and timing of medication reminders. Overall, there was a general consensus that it would be best if the messages did not contain the instruction and dosage of prescribed drugs and were not sent right before each medication. A detailed final refinement of the mHealth medication reminder intervention can be found in Table 6.5 in Section 6.1.3.

Moreover, it was not just about poor electronic health infrastructure they identified as healthcare system-related barriers in Iran. In this case, they argued that another complication may arise when both healthcare providers and patients, especially elderly patients, prefer traditional modes of post-discharge follow-up such as traditional face-to-face visits. They appear to show an understanding that a resistance to the use of information and communications technology in health from healthcare professionals may limit the ability to develop appropriate interventions for mobile health. According to Participant 22 in FG 3:

“The challenge is that most of the cardiac patients are in their 70s or 80s. They still prefer in-person physician visits and the direct contact with health professionals compared to remote contacts... Our doctors, nurses and other healthcare providers are not interested in using mobile health system to contact with their patients... because they do not receive related training”.

Participant 15 in FG 3 stated:

“It may be difficult to convince clinicians to follow-up with their patients using mHealth interventions as they always encourage patients to come into the hospital’s outpatient clinic; that is because they believe that this is where the quality care can be offered and they are less flexible to accept infrastructural changes in health care”.

The evidence from the participants in this study may suggest that to make the mHealth intervention appropriate to the Iranian setting, potential challenges need to be addressed prior to the intervention implementation. In addition to the aforementioned challenges, the nurse participants more specifically identified issues related to the mobile phone-based medication reminder intervention that seemed to play a big role in refinement and implementation of the intervention. This leads on to the next theme evident in the analysis.

Considerations before Implementation

Poor telecommunications coverage in some parts of the country and patients’ limited access to mobile phone devices were reported as some of the specific considerations for using mobile health interventions. Participant 5 in FG 1 said:

“You need to think about some issues before implementation of the text-message reminder intervention; Can you estimate, for example, if there are ten patients in a Cardiac Care Unit, how many of them own a mobile phone? I think only one or two !!...Moreover, there is no mobile signal in some remote areas”.

The sustainability of the programme was noted by some nurses in FGs as another consideration in the intervention development. Their concern was that patients may get used to or feel bored by reminders over time indicating that text messages may be ignored. However, the nurses were not so explicitly seen to be concerned about the development of dependency on receiving text message reminders among patients. It was not clear for them if the programme can be used long term. The following is a selected quote of a participant:

“I am not sure that how long patients need to receive those reminders?...they may get used to the messages...they may become tired of always repeating reminders”. (Participant 14, FG 3)

Participants in all FGs put forward a range of recommendations for the best implementation of the mobile health intervention including assessing the intervention

appropriateness, piloting or small-scale implementation of the intervention and tailoring the intervention to fit the purpose.

Intervention Acceptability

There was a united consensus that assessing the appropriateness of the intervention for the Iranian context is needed prior to the initial evaluation of the intervention. Participants indicated that it would be better to conduct a preliminary study on cardiac patients. They stated that an initial assessment may help explore the pattern of ownership, use of mobile phones and acceptability of using mobile phones as an adherence aid, and explore patients' perceptions and preferences about a potential mobile phone-based intervention to improve medication adherence. According to Participant 12 in FG 2:

"I think it is better to ask our patients first...ask them in a survey, for example, ...would you like to receive text-message reminders?...Is it useful for you? or what do you prefer to get from this intervention?..."

Participant 6 in FG 1 said:

"It is not clear that this kind of interventions using mobile phones really work here in this setting...can patients really use it?...are they interested?... we need to know whether all patients have their own mobile phone...have they ever used the text message on their mobile phones?"

Some participants also elaborated a concern that patients may share their phones with family. They suggested sharing of mobile phones may present a drawback in its use in health care:

" I quite often see some patients share their mobile phone with their elder son... Sending reminders is just for the patient... I think it may be bothering for the person who is using the phone at the same time..."(Participant 14, FG 3)

Taking everything into account, there was a general agreement that an initial patients' survey would be helpful to best design of the intervention prior to its implementation. To identify technical issues related to the intervention, it was suggested to make a weekly or biweekly phone calls and ask patients whether they face any problem in receiving text message reminders.

Pilot/ Small Scale Implementation

Most of the participants explained that there is a lack of pilot projects or small implementations of mHealth-based interventions in healthcare centres in Iran. They stated that a feasibility study is an important step that is helpful in understanding potential programmatic problems and the initial effect of the applied intervention before any large-scale evaluation. Following quotes indicated participants' suggestions regarding pilot implementation of the intervention:

“Since there is not enough evidence that shows what can mHealth do for patients ...you need to test this intervention in a small number of patients or a pilot group...Then you will find what’s the effect, problems, and the patients’ reactions...how it works for different patients...”(Participant 1, FG1).

“You can’t just bring a new intervention and say ok! let’s see what’s the effect...Full trials are usually very expensive...it is better at first to examine the feasibility of the programme in this particular setting...to see if any adjustments or adaptations to the programme are needed. Some unpredicted problems may happen during implementation such as issues with the setting, logistics and even evaluation of the outcomes; patients or even staff training may be necessary” (Participant 7, FG2).

The participants described that the pilot implementation of the programme provides initial information about positive effects the intervention may have on cardiac patients that can be shared with stakeholders, funders and policymakers. They also appear to have a positive insight into piloting the intervention among Iranian patients since they perceived it as a good opportunity to begin building an awareness and strengthening key partnerships, which will be important and helpful for a successful further implementation. According to Participant 16 in FG 3:

“Early findings from your pilot study may indicate whether the patients enjoy the mHealth medication reminders? Or is there any improvement in the medication adherence of the participants as an outcome of interest? Then you can disseminate or share this information about your programme that is for example well-received with your patients...there will be lessons to learn for your larger study, as well”.

Above-mentioned quotes also indicated that a pilot test can highlight any adjustments to the evaluation plan that might be necessary to ensure the desired outcomes are evaluated in the best way possible. This may suggest that the participants appreciate the importance of piloting the mHealth intervention. They acknowledged that a pilot study provides a chance to evaluate the effect of the

proposed intervention on a small sample of the target population in the Iranian setting before full implementation and troubleshoot any logistical issues that might arise with the collection of the data.

Intervention refinement

In addition to the above-mentioned suggestions regarding the assessment of the intervention acceptability and its small-scale testing prior to the full implementation, the participants also provided useful recommendations about the intervention refinement. They believed that it is better to refine the intervention to make it appropriate for patients who have been prescribed new medications in order to assist them in developing a routine. Participant 10 in FG 2 described why patients who have newly started cardiac medications may benefit more from the automated reminders:

“In my opinion, sending reminders for newly prescribed medications would be useful; you see, for example, some patients are taking their blood pressure medications for more than ten years. It becomes a habit to take those pills.. but if a new medication starts for them, they take them like one week but after that, they are more likely to forget them”.

A few number of participants also suggested using other mediums such as voice message, phone calls and emails with mobile phone reminders:

“Most patients may ignore text messages or turn off their phones when they’re driving or working so I think it would be better if you call them or send an email in addition to sending text reminders.” (Participant 4, FG 1)

In response to this suggestion, it was agreed to brief patients in the first visit about the importance of medication reminders and keeping their phones on during the course of the study. Participant 5 in the same FG said:

“There is not enough staff to phone all patients...it will be really time-consuming...I prefer mobile reminders that are automated. You need to brief your patients at the start point and stress on the importance of reminders so that patients know that they should not ignore text messages.”

With regards to the frequency of the messages, some participants felt that it is not necessary to send these messages right before or at the time patients are likely to be taking their medications. They reasoned that patients may feel bored and ignore

repeated messages over time. Moreover, sending reminders before each medication may cause dependency to the programme:

“You don’t want your patients to be dependent on these reminders, right? So, you don’t need to send them before each medication. They may get bored over time and even I can say they do not open the messages anymore”. (Participant 10, FG 2)

The evidence from the participants in this study show that although the nurses perceived the mHealth intervention positively, they were aware of potential obstacles to its implementation in the Iranian settings that need to be tackled in different ways. Considering the recommendations of the nurse participants regarding the refinement of the medication reminder intervention to make it appropriate to the local context, modifications were applied to the intervention prior to the exploratory trial phase (see Table 6.5).

6.1.3 Summary of the Phase 1 Results

The results of the CHD patients’ perception survey presents the acceptability of using mHealth text message reminder interventions to improve medication adherence for this group of patients in an Iranian setting. Mobile phone ownership and the use of text messages were relatively high among the respondents of the survey indicating that using an automated daily medication reminder in this format, might be the most acceptable intervention in this context.

In addition to the patients’ perception survey, the intervention was informed by qualitative focus groups findings that explored Iranian cardiac nurses’ perception about the potential effect, barriers and facilitators to implementation of the mHealth intervention in the Iranian settings. The emerging data from the focus groups identified three key themes of relevance as identified by the nurse participants including “positive impacts”, “unpreparedness for mHealth implementation” and “considerations before implementation”. The nurses perceived the intervention as being beneficial to CHD patients and their medication taking. The major benefits outlined in discussions were that the intervention would provide patients with reminders, connect hospital to home and prevent negative outcomes. Subthemes related to the unpreparedness to implement mHealth interventions included lack of IT knowledge among patients and healthcare providers, legal ambiguity and healthcare system-related barriers. The nurses also expressed their opinions and

recommendations about the refinement of the mHealth reminder intervention. The majority of participants suggested surveying patients and conducting a pilot study to have a better understanding of feasibility and acceptability of the intervention. They also provided suggestions about following-up with patients using other mediums along with text messages as well as pragmatic considerations in developing text message reminders (e.g. less frequent text messages to prevent patients' dependency and fatigue over time). Table 6.5 presents the number of refinements that were identified from the results of the first phase to make the intervention appropriate to the Iranian context.

Table 6.5. Description of the modified SMS intervention used in the present study based on the Modelling Phase recommendations

Modelling Phase Recommendations	Description of the modified SMS intervention used in the present study	Comparison with the original intervention in the previous study (Master's research)
<u>1. Patients' Perceptions (Survey Findings):</u>		No patients' perception survey was conducted in the previous study.
1.1 Preferred method of delivery: mobile phone text message	Method of delivery: mobile phone text message	Method of delivery: mobile phone text message
1.2 Preferred frequencies to receive text message reminders: "as often as the medications need to be taken" (50.4 %) and "once a day" (28.5%)	Frequency: once a day Note: see item 2.1 that clarifies the reason for choosing this option instead of the majority of the patients' preference)	Frequency: before every cardio-protective medication
1.3 Preferred timing to receive text message reminders: just before the medication time (44.7%) and every morning (6 am – 10 am) (16.3%)	Timing: every morning (8am) Note: see item 2.1 that clarifies the reason for choosing this option instead of the majority of the patients' preference)	Timing: according to the timing of medications
1.4 Preferred reminder contents: short and simple with general (not personalised) content	Content: short and simple with general (not personalised): <i>"Please, don't forget to take your medications"</i> .	Content: personalised to the patients' names and medications
1.5 Preferred 1-way reminders (not interested in sending a reply message to each reminder)	It was not mandatory for participants to send reply message to each reminder.	It was not mandatory for participants to send reply message to each reminder.

Modelling Phase Recommendations	Description of the modified SMS intervention used in the present study	Comparison with the original intervention in the previous study (Master's research)
<u>2. Nurses' Perceptions (Focus Groups Findings):</u>		No Focus groups was conducted in the previous study.
2.1 Due to the lack of shared electronic health system in Iran, there was a general consensus that it would be best if the messages did not contain the instruction and dosage of prescribed drugs and were not sent right before each medication.	See items 1.2 and 1.4	The messages contained the instruction and dosage of prescribed drugs and sent right before each medication.
2.2 Ethical considerations (e.g. to protect patients' mobile phone numbers against third-party telemarketers)	Steps undertaken to address ethical concerns are presented in Section 5.4; it was agreed with the TM service provider that patients' phone numbers would not be sold/ passed on to a third party without explicit consent (Appendix 16).	Similar to the present study.
2.3 To conduct a preliminary survey study among cardiac patients to explore the pattern of ownership, use of mobile phones and acceptability of using mobile phones as an adherence aid	A self-completion survey conducted among male and female CHD patients, aged 18 and over in one hospital affiliated to Tehran University of Medical Sciences (Section 5.2.1).	No patients' perception survey was conducted in the previous study.
2.4 To conduct a feasibility pilot study to identify the intervention programmatic problems and its initial effect before any large-scale evaluation	A 12-week pilot RCT, two-arm, pretest-posttest, with an equivalent comparison group was conducted among male and female Iranian CR patients of one Cardiovascular, Medical and Research Centre affiliated to Tehran University of Medical Sciences as a part of exploratory phase of the study (Section 5.3).	An 8-week pilot RCT, two-arm, pretest-posttest, with an equivalent comparison group was conducted among male and female Malaysian ACS patients of a tertiary hospital in Kuala Lumpur.
2.5 To consider poor telecommunications coverage in remote areas and other technical issues that may prevent delivery of text messages	The researcher followed up with the participants in the intervention group via telephone calls once per two weeks during the study to reassure the delivery of reminders.	Similar to the present study.

Modelling Phase Recommendations	Description of the modified SMS intervention used in the present study	Comparison with the original intervention in the previous study (Master's research)
2.6 To include patients who are newly prescribed cardioprotective medications	Newly diagnosed CHD patients participating in CR were recruited to receive/ not receive reminders for their cardio-protective medications.	Newly diagnosed CHD patients were recruited immediately after hospital discharge to receive/ not receive reminders for their cardio-protective medications.
2.7 To use other mediums such as voice message, phone calls and emails with mobile phone reminders	See item 2.5	Similar to the present study.
2.8 To consider patients may feel bored, turn off the device or ignore repeated messages over time	All participants were fully informed about this research, such as its purpose and process both verbally and written by providing participants' information sheets. During the first visit and over the biweekly phone calls, the importance of medication reminders and keeping the mobile phones on to receive text messages were emphasised.	Similar to the present study.
2.9 To send less frequent text message reminders (e.g. once a day)	See item 1.2	More frequent reminders were sent (i.e.before every cardio-protective medication) compared to the present study.

6.2 Exploratory Trial (Phase 2) Results

After remodelling the proposed mHealth intervention based on the survey and qualitative FGDs findings, the modified SMS intervention was piloted to investigate its effect on cardioprotective medication adherence during the second phase of the study through a RCT. The RCT sought to explore:

- The effect of a 12-week mHealth intervention on medication adherence of Iranian male and female CHD patients participating in CR (Objective 5);
- The effect of a 12-week mHealth intervention on the secondary outcomes: Medication Adherence Self-Efficacy (MASE); Cardiac Ejection Fraction (EF); Cardiac Functional Capacity (FC); CHD-related Readmission/Mortality Rate and Health-related Quality of Life (HR-QOL) of Iranian male and female CHD patients participating in CR (Objective 6);

- The association between socio-demographic factors of the subjects and medication adherence in both intervention and control groups (Objective 7);
- The perception of participants in the intervention group towards the received mHealth intervention at the end of the study (Objective 8).
- The recruitment and retention rate and inform the sample sizes required for a further larger trial (Objective 9).

6.2.1 Participants Flow and Follow-up

During the recruitment period (February 2016), a total of 98 CR patients were newly admitted to the outpatient CR clinic. Among them, 3 patients refused to participate in the study, and 17 of them were excluded. Reasons for exclusion included being severely ill (n=2) and having travel commitments (n=15). Hence, 78 (76.4%) eligible patients consented to participate in the study and were randomly assigned to control (n=39) and intervention groups (n=39). There were 3 dropouts after 12-week follow-up, 1 in the control and 2 in the intervention groups due to the patients' hospitalisation for a surgery. In total, 75 (~96%) patients completed their participation; they were followed up and data were analysed for these patients in this study. Figure 6.1 presents the flow diagram of the study based on the Consolidated Standards of Reporting Trials (CONSORT) (2010).

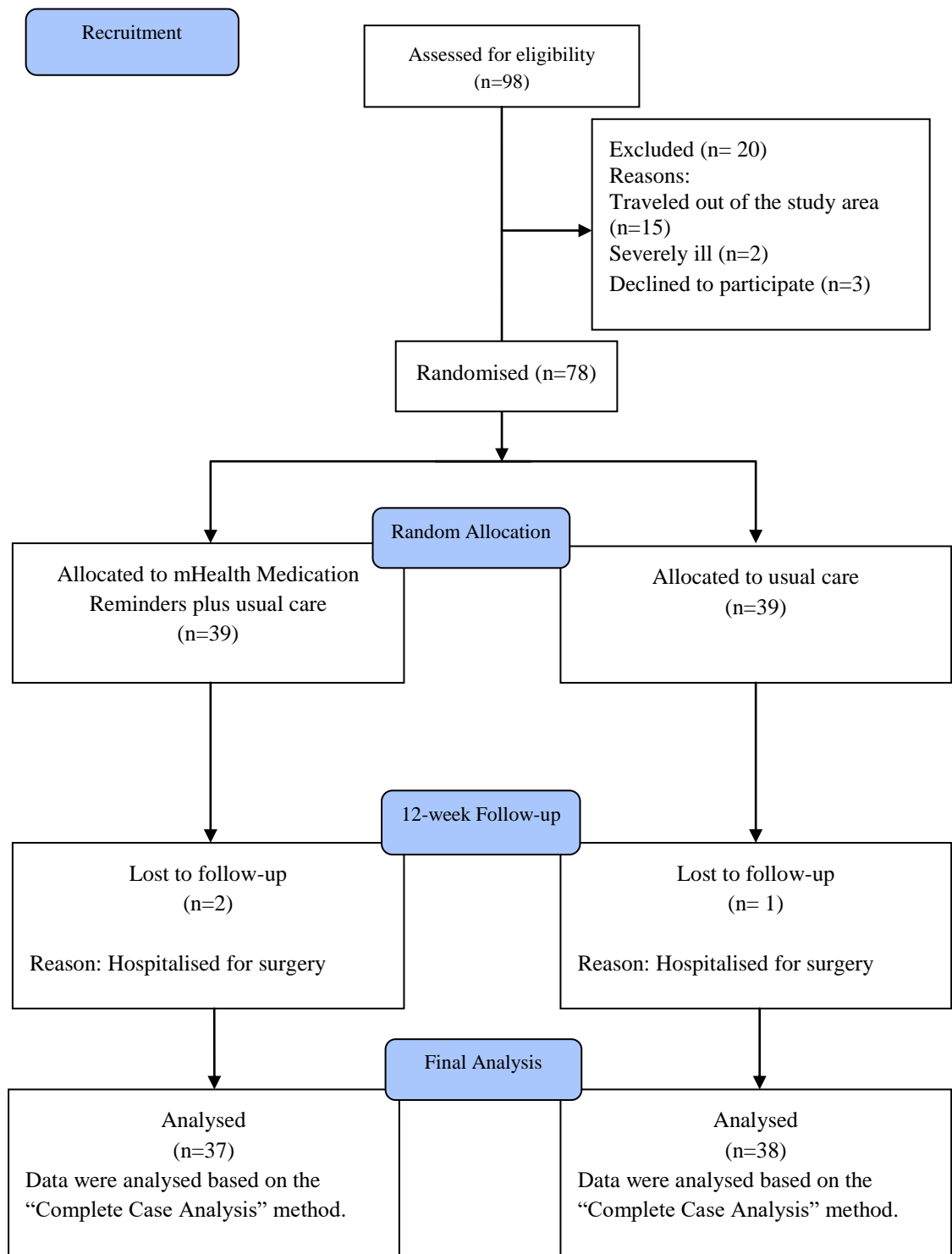


Figure 6.1. CONSORT Flow diagram of the study

A total of 3510 SMS reminders were sent to all 39 patients in the intervention group (90 SMS reminders/ patient over the 12-week intervention period). From the total number, 2943 (83.84%) successful delivery reports were received. The delivery status of 543 (15.47%) messages was not recorded in the system. Although participants were not required to do so, some texted in during the first month of the study, notifying that they had taken their medications for the prior days (e.g. “took medication today, thank you”) (Mean 2.28 text messages, SD±3.02, Range: 0–10, over the first 4 weeks of the study period). The last follow-up visit occurred on June 6, 2016. Of 78 patients, 75 (96.15%) were visited approximately 12 weeks after the study start-point while the other 3 patients had been hospitalised for a surgery in a hospital other than the study setting.

6.2.2 Characteristics of Participants

Characteristics of all 78 participants are shown in Table 6.6. All variables were similar between study groups with no statistically significant differences.

Table 6.6. Characteristics of pilot RCT participants (n=78)^a

Characteristics	Overall (n=78)	Intervention (n=39)	Usual care (n=39)	P value ^b
Age, mean (±SD), years	61.87 (±1.02)	60.44 (±1.57)	63.31 (±1.29)	0.16
Sex				1
Male	56 (71.8)	28 (71.8)	28 (71.8)	
Female	22 (28.2)	11 (28.2)	11 (28.2)	
Education				0.43
Primary	27 (34.6)	13 (33.3)	14 (35.9)	
Secondary	26 (33.3)	11 (28.2)	15 (38.5)	
University	25 (32.1)	15 (38.5)	10 (25.6)	
Marital status				1
Married	74 (94.9)	37 (94.9)	37 (94.9)	
Single	4 (5.1)	2 (5.1)	2 (5.1)	
Employment				0.61
Employed	19 (24.4)	9 (23.1)	10 (25.6)	
Unemployed/ Housewife	17 (21.8)	7 (17.9)	10 (25.6)	
Retired	42 (53.8)	23 (59)	19 (48.7)	
Monthly Income				0.67
Enough	19 (24.4)	10 (25.6)	9 (23.1)	
Quite Enough	41 (52.6)	22 (56.4)	19 (48.7)	
Not Enough	17 (21.8)	7 (17.9)	10 (25.6)	
No Answer	1 (1.3)	-	1 (2.6)	

Characteristics	Overall (n=78)	Intervention (n=39)	Usual care (n=39)	P value ^b
Living arrangement				1
With family	77 (98.7)	38 (97.4)	39 (100)	
Alone	1 (1.3)	1 (2.6)	0	
Family Size				0.19
≤2	31 (39.7)	12 (30.8)	19 (48.7)	
3-4	40 (51.3)	24 (61.5)	16 (41)	
≥5	7 (9)	3 (7.7)	4 (10.3)	
Diagnosis				0.17
Post-Revascularisation	68 (87.2)	32 (82.1)	36 (92.3)	
ACS & Others	10 (12.8)	7 (17.9)	3 (7.7)	
Diagnosis Time				0.22
<1 year ago	49 (65.3)	24 (64.9)	25 (65.8)	
2-5 years ago	9 (12)	6 (16.2)	3 (7.9)	
>5 years ago	17 (22.7)	7 (18.9)	10 (26.3)	
Co-morbid				0.23
Yes	64 (82.1)	30 (76.9)	34 (87.2)	
No	14 (17.9)	9 (23.1)	5 (12.8)	
Hospital Stay, mean (±SD), days	13.29 (±0.74)	12.38 (±6.78)	14.21 (±6.37)	0.18
Medication Adherence, mean (±SD)	6.31 (±0.11)	6.21 (±0.16)	6.41 (±0.16)	0.35
Low (<6)	16 (20.5)	11 (28.2)	5 (12.8)	0.09
Medium (6-<8)	62 (79.5)	28 (71.8)	34 (87.2)	
High (=8)	-	-	-	
Functional Capacity				0.47
High	-	-	-	
Good	70 (89.7)	34 (87.2)	36 (92.3)	
Average	6 (7.7)	4 (10.3)	2 (5.1)	
Fair	2 (2.6)	1 (2.6)	1 (2.6)	
Ejection Fraction, mean (±SD)	48.05 (±0.97)	48.55 (±6.35)	47.56 (±10.31)	0.67
MA Self Efficacy, mean (±SD)	2.53 (±0.34)	2.45 (±0.34)	2.6 (±0.33)	0.05
PCS ^c , mean (±SD)	42.15 (±0.82)	43.43 (±1.07)	40.87 (±1.21)	0.12
MCS ^d , mean (±SD)	47.41 (±1.3)	46.72 (±1.76)	48.1 (±1.9)	0.6

SD: Standard Deviation; ACS: Acute Coronary Syndrome; MA: Medication Adherence; PCS: Physical Component Summary; MCS: Mental Component Summary

a. Data are presented as frequency (percentage) unless otherwise specified.

b. Usual care group vs. intervention group.

6.2.3 Medication Adherence (Objective 5)

A self-report of medication adherence (MMAS-8-item) was used to measure medication adherence level at baseline and follow-up. The objective was to test if there was a significant difference in medication adherence level between the control

and intervention groups. It was found that 56.8% of participants in the intervention group who received SMS-reminders to take their medications had a high level of adherence compared to 5.3% of those in the usual care group. The majority of the patients in the control group had a medium adherence level to their cardiac medications (Table 6.7). The data are presented graphically in Figure 6.2.

There was a highly significant difference in medication adherence levels between the control and intervention groups, $\chi^2 (2) = 23.447$; $P < 0.001$. The Relative Risk was indicated that it is 2.19 times more likely for the control group to be less adherent to their medications than the intervention group (Relative Risk = 2.19; 95% CI 1.5 - 3.19).

There was also a significant positive change in the patients' medication adherence in the intervention group prior to and following the study ($Z = -2.84$; $P < 0.001$) while the control group did not show a significant improvement over time of the study ($Z = -0.08$; $P = 0.93$).

Table 6.7. Medication adherence at baseline and post-test data collection

Study Groups	Study Time	Medication Adherence (%)		
		Low	Medium	High
Intervention (n=37)	Baseline	27	73	0
	Post-test	8.1	35.1	56.8
Control (n=38)	Baseline	13.2	86.8	0
	Post-test	21.1	73.7	5.3

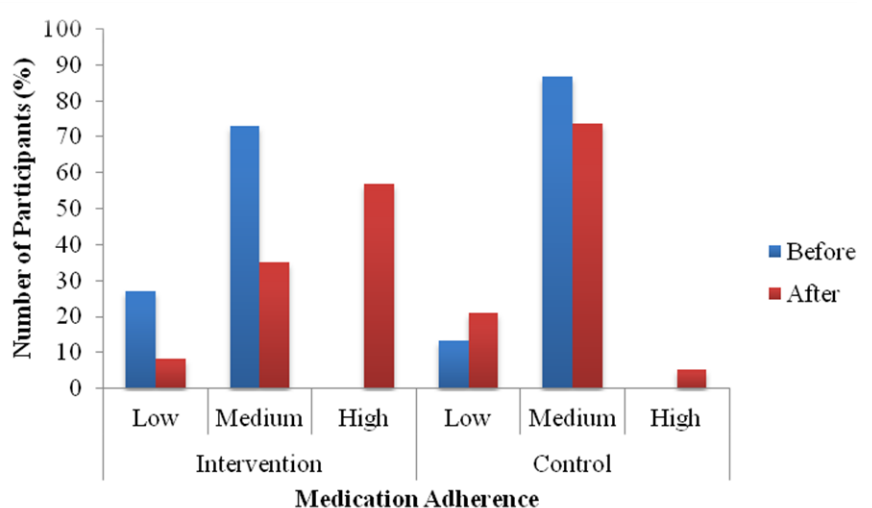


Figure 6.2 Medication adherence changes before and after the study within each study group

6.2.4 Medication Adherence Self-Efficacy (Objective 6)

Another study objective was to test if there was a significant difference in patients' Medication Adherence Self-Efficacy (MASE) between the control and intervention groups. The mean, Standard Deviation (SD), and median values for each of the groups studied in the experiment at recruitment and post-test data collection are presented in Table 6.8. A graph of the mean differences is also presented in Figure 6.3.

Table 6.8. Medication Adherence Self-Efficacy at baseline and post-test data collection

Study Group	Study Time	Mean	Std. Deviation	Median
Intervention (n=37)	Baseline	2.45	0.34	2.57
	Post-test	2.68	0.31	2.76
Control (n=38)	Baseline	2.6	0.33	2.63
	Post-test	2.29	0.65	2.46

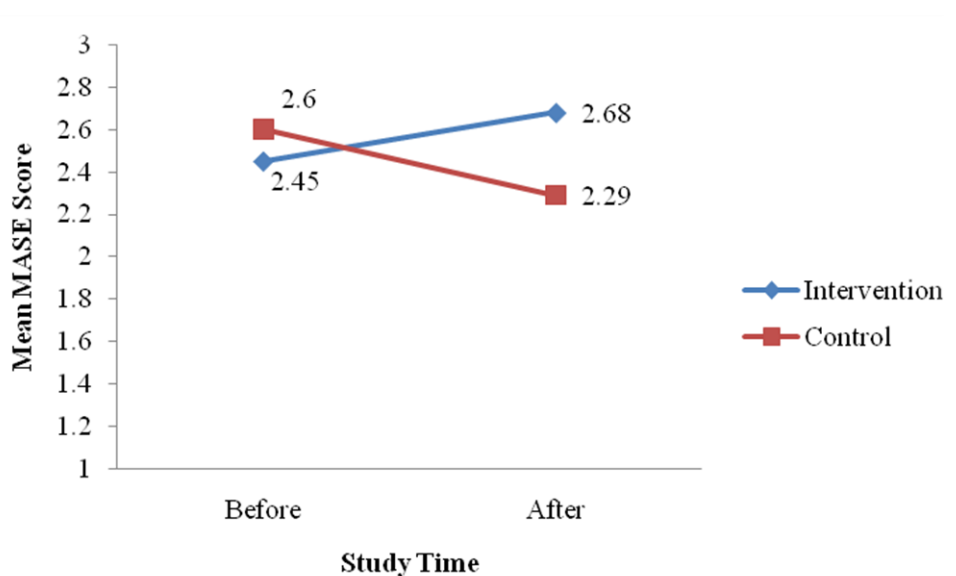


Figure 6.3. Mean MASE scores before and after the study within each study group

In the analysis of the differences in changes of MASE, a Mann-Whitney U test indicated that MASE scores were statistically significantly greater for the intervention group that was receiving medication reminders than for those in the usual care group who were not receiving medication reminders ($U=505$; $P=0.035$).

In line with these significant difference between the study groups, the MASE scores of the intervention group had statistically significant improvement prior to and

following the study, ($Z=-3.18$; $P<0.001$). Conversely, patients in the control group experienced significant fall in their self-efficacy in taking cardiac medications over time of the study, ($Z =-1.98$; $P=0.04$).

6.2.5 Cardiac Ejection Fraction (Objective 6)

In the study of the differences in patients' cardiac Ejection Fraction (EF), the mean, SD, and median values for each of the groups studied in the experiment at recruitment and post-test data collection are presented in Table 6.9.

Table 6.9. Ejection Fraction at baseline and post-test data collection

Study Group	Study Time	Mean	Std. Deviation	Median
Intervention (n=37)	Baseline	47.43	6.62	50
	Post-test	49.35	6.27	50
Control (n=38)	Baseline	47.11	9.77	50
	Post-test	46.34	10.52	50

A Mann-Whitney U test was applied to investigate the differences in EF between the intervention and control groups that indicated no significant differences ($U=639.5$, $P=0.48$). Therefore, there is insufficient evidence of a difference in Cardiac EF of participants in the intervention group receiving medication reminders compared to the usual care group who were not receiving medication reminders.

There was a significant increase in EF of patients in the intervention group who received medication reminders between the pre-test and post-test data collection ($Z=-3.31$; $P<0.001$). Patients in the usual care group who were not receiving medication reminders demonstrated a reduction in EF prior and following the study that was not statistically significant ($Z =-1.22$; $P=0.22$).

6.2.6 Cardiac Functional Capacity (Objective 6)

One of the objectives of this study was to test if there is a significant difference in patients' cardiac Functional Capacity (FC) between the control and intervention groups. As can be seen from Figure 6.4, around 97% of participants in the intervention group had no symptoms and no limitations in ordinary physical activity compared to 65.8% of those in usual care group at the endpoint of the study.

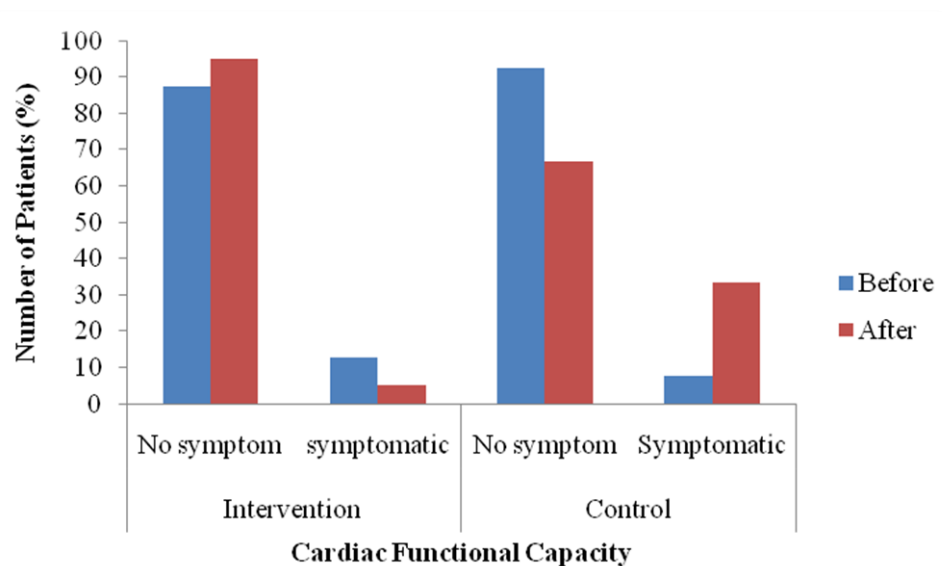


Figure 6.4. Cardiac FC changes before and after the study within each study group

The Chi-square test determined that there is a highly significant difference in cardiac FC between the control and intervention groups, $\chi^2 (1) = 9.722$, $P=0.002$. In order to determine any significant changes in FC classification in each group over the study period, the McNemar test was performed. It did not elicit statistically significant changes in FC among intervention group ($P=0.25$). Indeed, more than half of the patients who received reminders were categorised in high and good FC classifications both pre- and post-intervention. However, there were significant negative changes in FC among the control group ($P=0.006$). Around one-third of the patients in the control group who were assigned in good FC class at recruitment categorised in fair and poor classes at the endpoint of the study.

6.2.7 Hospital readmission and death rates (Objective 6)

CHD-related readmissions were defined as any readmission due to a chest pain or recurrent cardiac events based on the patients' hospital records as well as participants' confirmation. Although there are more readmissions in the control group ($n=3$) compared to the intervention group ($n=1$), the p-value of the difference in the number of readmissions between the study groups for the Fisher's Exact was 0.61, which is not statistically significant. It indicates that there is no significant difference in the number of readmissions between the study groups. No death occurred among patients in either group.

6.2.8 Health-related Quality of Life (Objective 6)

In order to evaluate the Health-related Quality of Life (HR-QOL), two questionnaires, one pre-test, one post-test, were completed by all participants. Two scores including Physical and Mental Component Summary, PCS and MCS, were calculated (Range: 0-100) according to the instructions provided in the questionnaire's user manual; a high score corresponded to a better state of health. The mean, SD, and median values of PCS and MCS for each of the groups studied in the experiment at recruitment and post-test data collection are presented in Table 6.10 and 6.11, respectively. Linear graphs of these values are presented in Figure 6.5 and 6.6.

Table 6.10. Physical Component Summary at baseline and post-test data collection

Study Group	Study Time	Mean	Std. Deviation	Median
Intervention (n=37)	Baseline	43.19	6.75	42.45
	Post-test	47.46	6.97	48.08
Control (n=38)	Baseline	41.13	7.52	41.45
	Post-test	44.41	8.81	42.62

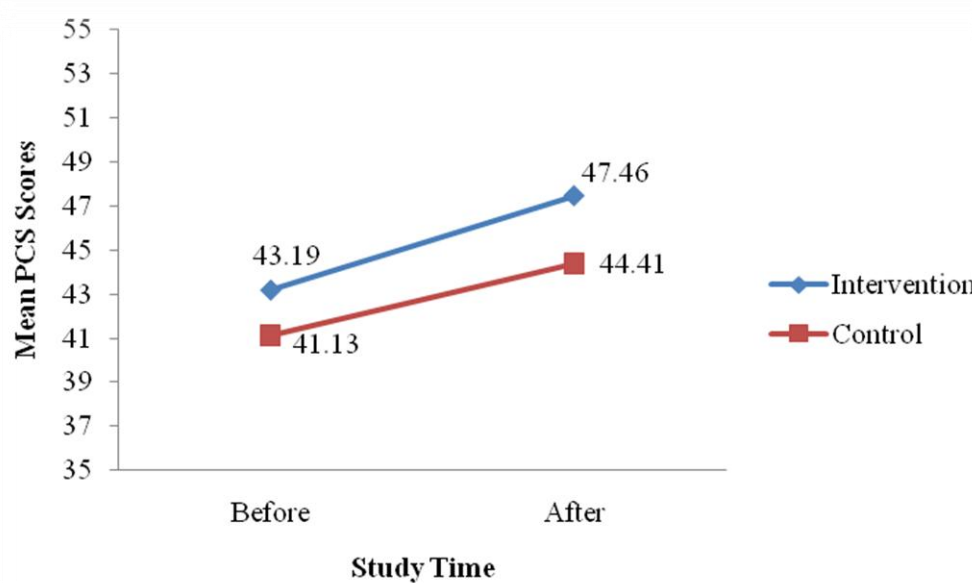


Figure 6.5. Physical Component Summary changes before and after the study within each study group

Table 6.11. Mental Component Summary at baseline and post-test data collection

Study Group	Study Time	Mean	Std. Deviation	Median
Intervention (n=37)	Baseline	46.78	11.24	45.71
	Post-test	49.34	11.23	48.63
Control (n=38)	Baseline	47.51	11.42	46.5
	Post-test	47.99	8.27	48.66

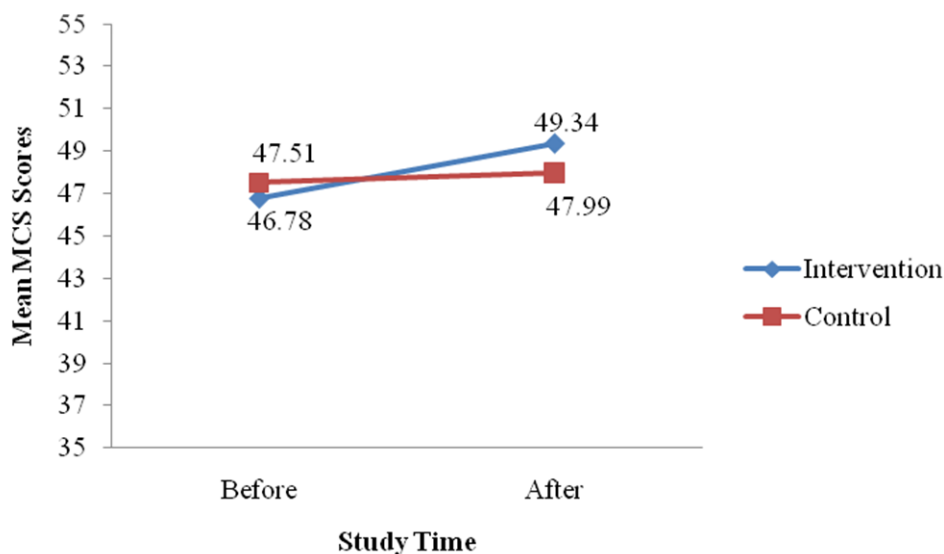


Figure 6.6. Mental Component Summary changes before and after the study within each study group

The normality of the distribution of scores for PCS and MCS scores was confirmed with the Kolmogorov-Smirnov test. Then, the independent samples t-test was used to estimate the between-group difference in each subscale of HR-QOL. The PCS mean difference between groups was -3.04, 95% CI: -6.71- 0.61. Although the mean PCS of the intervention group (47.46, $SD\pm 6.97$) was greater than the control group (44.41, $SD\pm 8.81$), the two-tailed P-value of the test was 0.1. Thus, there was no statistically significant difference in the mean PCS between the two study groups. The MCS showed no significant effect of the intervention, as well ($P=0.55$).

At recruitment time, participants in both groups reported an impaired physical functioning and an average mental wellbeing based on their PCS and MCS scores. At 3 months, an improved HR-QOL was found in both study groups in comparison with the study baseline. Both groups had a significant improvement in the PCS of the

questionnaire, with a difference of -3.28 points (95% CI -6.4 to -0.08) in the control group and -4.26 (95% CI -7.14 to -1.39) in the intervention group. There was no statistically significant improvement in the MCS scores within each study group over time.

6.2.9 Participants' Demographic Characteristics and Medication Adherence (Objective 7)

One of the study objectives was to identify the association between participants' demographic characteristics and medication adherence in both intervention and control group. The Multiple Logistic Regression was applied to test the hypothesis that a particular factor/variable predicts the outcome of medication adherence. The study of the association between participants' characteristics and medication adherence indicated that socio-demographic data had no significant relationship with medication adherence (see Table 6.12).

Table 6.12. Participants' characteristics and medication adherence level

Variable	Chi-square value	P value	Exp (B)	95% CI for Exp (B)	
				Lower Bound	Upper Bound
Age	0.093*	0.58	0.42	0.055	3.182
Sex	0.923	0.337	1.749	0.555	5.510
Education	<0.001	0.989	0.993	0.354	2.783
Marital status	0.656*	0.306	1.479	1.259	1.738
Employment	0.307	0.579	1.425	0.406	5.006
Living arrangement	<0.001*	1	0.689	0.591	0.803
Monthly Income	0.029	0.865	0.903	0.276	2.948
Family Size	<0.001*	1	0.895	0.161	4.993
Diagnosis	0.913	0.339	1.979	0.479	8.176
Diagnosis Time	1.137	0.286	1.731	0.628	4.767
Co-morbid	0.206	0.65	0.753	0.222	2.562
Hospital Stay	2.81	0.094	0.423	0.153	1.17
Daily Medications	0.948	0.33	1.676	0.59	4.765

*Yates' continuity correction value.

6.2.10 Patients' Perceptions about the Intervention (Objective 8)

The majority of participants who received the intervention (28/39 or 71.8%) said the SMS reminders for taking medications were useful. Just over one-fifth of participants felt that it had helped them as a reminder to take their medications. They also reported SMS messages was not just a reminder; the intervention helped them in a variety of aspects including feeling support, maintaining interaction with healthcare system, promoting independence and self-efficacy in taking medications.

Over 60% of participants strongly agreed / agreed SMS medication reminders should be continued in the future. Participants in the intervention group (~60%) also strongly agreed/ agreed to suggest SMS medication reminders to other patients. Almost 75% of patients perceived the intervention did not cause any intrusion into their life.

Patients were asked for their recommendations to improve the intervention. Almost half of them reported their satisfaction with the same intervention component. Table 6.13 presents the details of the patients' perceptions about the applied mHealth intervention.

Table 6.13. Patients perceptions about the applied mHealth intervention (n=39)

Perceptions Items	n (%)
Opinion on SMS reminders for taking medications	
Useful	28 (71.8)
No difference	4 (10.3)
Not useful	1 (2.6)
No answer	6 (15.4)
In which aspect this service help	
As reminder (prevent forgetfulness)	8 (20.5)
Feeling support	7 (17.9)
Keeping interaction with healthcare system	3 (7.7)
Maintaining independence/ self-efficacy in taking medications	2 (5.1)
All mentioned above	12 (30.8)
No answer	7 (17.9)
Want the SMS reminder to be continued in future	
Strongly Agree	15 (38.5)
Agree	9 (23.1)
Neutral	8 (20.5)
Disagree	-
Strongly Disagree	-
No answer	7 (17.9)

Perceptions Items	n (%)
Suggest this SMS reminder to other patients	
Strongly Agree	12 (30.8)
Agree	11 (28.2)
Neutral	9 (23.1)
Disagree	1 (2.6)
Strongly Disagree	-
No answer	6 (15.4)
SMS reminders may cause intrusion into a person's life	
Strongly Agree	-
Agree	3 (7.7)
Neutral	1 (2.6)
Disagree	-
Strongly Disagree	29 (74.4)
No answer	6 (15.4)
Would you pay to receive SMS reminders, if required?	
Strongly Agree	11 (28.2)
Agree	-
Neutral	7 (17.9)
Disagree	15 (38.5)
Strongly Disagree	-
No answer	6(15.4)
What are your recommendations to improve this service in future?	
As perfect as it is (no changes needed)	10 (25.6)
To be tailored to patients' needs/ just for one specific medication	3 (7.7)
To offer free of charge	2 (5.1)
To be sent before every medication	1 (2.6)
To be sent more than once a day	1 (2.6)
To include health-related advice	1 (2.6)
No answer	21 (53.8)

6.2.11 Findings to Inform Future Definitive Large-scale RCT (Objective 9)

One of the objectives of this pilot study was to determine recruitment, retention rate and the effect size obtained by this pilot to inform the sample size calculation for a future definitive RCT.

Estimating Recruitment and Retention

The initial strategy to identify participants was to approach CHD patients who were admitted for the first time to the outpatient CR clinic in a university-affiliated hospital in Teharn. To this end the researcher spoke with the CR clinic manager, the head nurse and the clinic administrator in several meetings. This proved a very effective route for recruitment and it also helped to enhance awareness of the study

and enabled the researcher to collect information on approaches to optimise recruitment and retention. A separate room in the CR clinic was allocated as recruitment area for baseline and follow-up visits, and patients were visited at the same day of their outpatient cardiology clinic appointment in the same building to prevent additional travelling between home and hospitals. It was estimated that the baseline and follow-up face-to-face visits to assess primary and secondary outcomes took no more than 10 minutes. This approach seemed to work well and indicated feasibility of recruitment. No financial incentives were offered to the patients. The attrition rate was 3.8% with the reason for loss to follow-up readmission for surgery.

Determining Sample Size

The intervention showed significant effect on improving cardiovascular medication adherence (i.e. the study primary outcome) among CHD patients in the CR setting in Iran. A relatively large effect (Relative Risk = 2.19; 95% CI 1.5 - 3.19) was found on medication adherence. The results of the pilot informed the sample size needed for a future definitive RCT. A sample size of 130 patients per group (260 in total) is required to have 90% power to detect a realistic difference of 20% or greater for the between-group percentage of patients with high adherence to their medication in a future study, assuming a (two-sided) 5% significance level.

CHAPTER 7: DISCUSSION AND CONCLUSION

The results that were presented in Chapter 6 will be discussed and interpreted in relation to the objectives of the study and existing literature. This Chapter will provide a comparison of the study findings with previous similar research studies, the strength and limitations of the study and the implications of the findings at micro-level (patients and providers), meso-level (healthcare organisation) and macro-level (health policy). At the end of this Chapter, the conclusion of this research study will be presented, as well.

The overall aim and specific objectives of the study were developed and the method of investigation selected following a review of the literature related to the development and evaluation of the mHealth interventions to promote medication adherence and the theories relevant to behavioural change interventions. The study aimed to develop and evaluate a nurse-led mHealth intervention to promote medication adherence in Iranian CHD patients who presented in Cardiac Rehabilitation (CR) clinic. The study phases (i.e. the Preclinical, Modelling Phase and the Exploratory Trial Phase) were developed based on the Medical Research Council's (MRC) Framework on the development and evaluation of complex interventions. In order to ensure that the intervention would be fit for purpose (i.e. to capture fidelity of the intervention) and inform a future definitive RCT, it was necessary to apply the MRC framework to develop and refine the intervention. The first step (the Preclinical and Modelling Phase) was establishing the theory and evidence for developing a nurse-led mHealth intervention to promote cardiovascular medication adherence. The World Health Organisation (WHO) Adherence Model and Self-efficacy Theory were applied as guides in the refinement of the study intervention (i.e. the automated SMS medication reminder). Based on the MRC framework, a feasibility and piloting phase is recommended after the development of a new intervention (Arain et al., 2010, Craig et al., 2011). Therefore, in order to understand the feasibility of the intended intervention and make it appropriate to the local context, a formative patients' perception survey and cardiac nurses' focus groups were conducted. In the Exploratory Trial Phase, the effect of the automated SMS medication reminder as a type of mHealth intervention was evaluated on

cardiovascular medication adherence in the particular setting of Iranian CR. The findings of this evaluation will also be discussed.

7.1 Interpretation of Results and Relationship to Previous Studies

The interpretation of results and comparison with previous studies will be presented according to each of the study objectives. The first findings to be discussed will be the ownership and utilisation of mobile phones in Iranian CHD patients followed by patients' perceptions about mHealth intervention as well as cardiac nurses' perception regarding the potential benefits and associated challenges of mHealth intervention in the Iranian context. Finally, the findings of the pilot RCT of the automated SMS medication reminder will be discussed.

7.1.1 Patients' Perceptions Survey Findings (Objective 1 and 2)

The results of patients' perception survey indicated that there is a high ownership of mobile phones among Iranian CHD patients (98.4%). In this patient group, a high use of the Short Message Service (SMS) function was found (68.3%). Interestingly, it was found that education was significantly associated with using SMS function and using mobile phones to connect to the internet, suggesting these functions may not commonly be used by patients with lower level of education attainment. This was consistent with a similar study that aimed to design a mobile phone intervention to improve Anti-Retroviral Therapy (ART) adherence in India (Shet et al., 2010). They reported education level as the only socio-demographic variable that had a significant association with using SMS, based on a self-completed survey of 322 Indians with Human Immunodeficiency Virus (HIV).

Owning a Smartphone (41.5%), using mobile phones to connect to the Internet (33.3%) and using the phone alarm function as a medication reminder (5.7%) were less common among the study participants. According to these findings, using a Smartphone application or a web-based intervention to improve medication adherence would be difficult to implement in an Iranian setting given the relatively low rates of Smartphone ownership and utilising of applications and the Internet. However, in contrast, participants reported higher levels of utilising SMS function; indicating it may be easier for patients to use SMS than Smartphone applications.

According to the International Telecommunication Union (2015), there were 74.22 million mobile phone subscribers (93.4 subscribers per 100 people) in Iran in the year 2015. Major operators in Iran including Mobile Telecommunication Company of Iran (MCI/Hamrahe Aval), Irancell, Taliya and RighTel serve more than 51 million mobile Subscriber Identity Module (SIM) cards associating with mobile phone penetration rate of 94.46% (International Telecommunication Union, 2015). In terms of accessibility to telecommunication services in rural areas, Iran has been given the United Nations Educational, Scientific and Cultural Organisation (UNESCO) special award (Tasnim News Agency, 2014). Costs of acquisition and using mobile phones in Iran are amongst the cheapest in the world (price of a basic mobile phone is around £19). Iranian main operators communicated more than 40 million text messages each day in early 2010 (Goodarzi et al., 2012). This arising telecommunication feature has the potential to implement new grounds of utilisations in health care for different reasons (Fjeldsoe et al., 2009, Cole-Lewis and Kershaw, 2010); the price is low, its use is extensive, and it is the simplest function accessible in even a basic model of mobile phone (Cole-Lewis and Kershaw, 2010, Dale et al., 2015). Therefore, a SMS-based medication reminder intervention may have the potential to be a feasible mHealth intervention in the particular context of Iranian CHD patients.

The survey study results showed that Iranian CHD patients perceived the mHealth intervention helpful to remind their prescribed medications. This finding is consistent with previous studies exploring the perception of patients with different chronic conditions about medication reminders. For example, Quilici et al. (2013) found that Acute Coronary Syndrome (ACS) patients who received unidirectional daily SMS reminders for aspirin intake perceived the intervention useful and acceptable (see Section 3.6). Another survey study on SMS reminders for ART treatment showed that the reminders were perceived by 139 Indian adult HIV patients to be useful in remembering medications (Sidney et al., 2012).

Issues related to intrusion of privacy were less reported to be a significant barrier to using mobile phones as an adherence support among Iranian cardiac patients whereas in contrast confidentiality issues were found to be very important in previous studies mostly among HIV participants in developing countries when using

mobile phone reminders (Crankshaw et al., 2010, Curioso et al., 2009). This finding highlighted the significance of context and culture-related issues in the development of a feasible and acceptable mHealth intervention and the nature of the condition begin treated.

The results also showed the importance of obtaining patients' preferences (shared decision making) about the timing, frequency and content of text message intervention before they were implemented. This is consistent with the findings from systematic reviews that found mHealth interventions must be flexible and be culturally and socially appropriate to the indication and to the needs of the patient (Gandapur et al., 2016, Kaplan, 2006). The majority of respondents preferred to receive a one-way SMS reminder either before each medication time or once a day in the morning with general content that simply remind them to take their medications. This informed the decision to formulate patient-preferred SMS content and develop an automated system to send each SMS reminder to patients' mobile phones every morning over the time of the study. Participants in this study also expressed their high interests in receiving the intervention for their cardiovascular medications.

7.1.2 Nurses' Perception about mHealth Interventions (Objective 3 and 4)

Although the intended mHealth intervention and its evaluations drew on existing theories (i.e. the WHO adherence model and the Bandura's self-efficacy theory), the intervention's refinement was driven by other factors, such as patients' (intervention recipients') preferences and relevant healthcare providers' (intervention deliverers') experiences. Hence, in addition to the patients' perception survey, focus groups were conducted with participation of Iranian cardiac nurses to explore their perspectives towards mHealth and to obtain suggestions for the best implementation of the automated SMS medication reminder intervention.

In this study, Iranian nurses perceived mHealth interventions as useful and can act as reminders to prevent patients' forgetfulness (as an important factor related to medication adherence in the WHO Adherence Model). In fact, nurses believed that the use of this intervention would be necessary as it has the potential to improve medication taking, patients' link to healthcare providers after discharge and reduce

post-discharge adverse outcomes and health care expenses related to medication nonadherence. The results are in line with the findings of previous studies, in which healthcare professionals have emphasised the necessity of applying eHealth (i.e. an overarching term that includes mHealth and teleHealth (Kay, 2011) in practice. For example, the study by Ayatollahi, et al. (2015) who explored Iranian clinicians' knowledge and perceptions of eHealth showed that the majority of respondents agreed with the essentiality of using eHealth to promote and facilitate the patients' accessibility to health care services. In another study, Sharifi, Ayat et al. (2013) conducted a literature review and qualitative interviews with 15 professional experts to identify eHealth implementation challenges in Iran. They found that the implementation of eHealth has the potential to improve patient access to health care, decrease total health expenses, and quality of care delivery. Another study by El-Mahalli et al. (2012) exploring the perceptions of health professionals in Saudi Arabia about teleHealth showed that the major perceived benefit of teleHealth adoption related to patients' follow-up after face-to-face contact. Therefore, the current findings are supported by the results of the previous studies that have emphasised the positive aspects of eHealth.

To develop a successful mHealth intervention, understanding the nature of challenges and barriers is needed. Using this knowledge and following thoughtful consideration, it is possible to predict potential challenges and barriers, develop a context-appropriate approach to address challenges, make proper modifications and ultimately implement the new intervention (Chaplin, 2008). In spite of the discussed potential advantages of mHealth, the findings from the focus groups also shed light on associated challenges to the implementation of the mobile health interventions in the context of Iran. Patients' and healthcare professionals' limited knowledge, legal challenges, security and privacy concerns, lack of a shared and interconnected electronic health records within hospitals and other healthcare settings in Iran were frequently expressed by the nurses. Some of these barriers to mHealth implementation resonate with another similar study. Ayatollahi, et al. (2015) reported that Iranian health care providers' knowledge of teleHealth was at a low or very low level which was an important obstacle for initiating a teleHealth programme. Regarding the security of teleHealth, they found that nurses were significantly more

concerned about the teleHealth security compared to physicians and specialists. When the nurses in the focus groups for this study were discussing their legal and security uncertainties in utilising mHealth in practice, they highlighted the need for a national guidance specifically for mHealth implementation to support nurses and address their ethical concerns. The National Code of Ethics for Nurses in Iran that has been compiled under the Ministry of Health and Medical Education (MOHME) supervision, outlines the nurses' ethical responsibilities in five parts in relation to people, nursing profession, practice, co-workers, education and research (Zahedi et al., 2013); however, there is limited guidance specifically about nurses' responsibilities on medication administration as well as eHealth implementation in practice. According to Sharifi Ayat et al. (2013), in Iran some pilot and small-scale eHealth projects have been initiated in the 2000s including gathering and recording health-related information of Iranian citizens which is still in the initial stages. They also extracted numerous factors related to the utilisation of eHealth from interview sessions with Iranian professionals including a lack of a comprehensive hospital information system, security and privacy issues for the protection of data, limited training and knowledge, legal concerns to protect both healthcare providers and patients (Sharifi et al., 2013). In another study conducted by Rezai-Rad et al. (2012), a framework was designed to assess eHealth implementation readiness in Iran; Based on the literature and opinions of 24 Iranian experts', privacy concerns, clinicians' and patients' information literacy and technology skills were perceived to have the highest priority in the utilisation of eHealth. The same challenges were reported in a review of eHealth in the Eastern Mediterranean Region (including Iran) indicating multiplicity and diversity of constraints in eHealth implementation in the Region (Al-Shorbaji, 2008). El-Mahalli et al. (2012), in their cross-sectional descriptive study showed that the major perceived barriers to the adoption of teleHealth from Arab health professionals' point of view were the limited health workers' knowledge and the lack of appropriate training about teleHealth.

Considering the acknowledged mHealth limitations, the nurses were asked to put forward recommendations and suggestions for optimising the design and evaluation of the study intervention (i.e. the automated SMS-based medication reminders). For example, the nurses emphasised that there is a lack of shared medical

information within Iranian hospitals and pharmacies and therefore it would be difficult to update SMS reminders in the case of prescription changes over the time of the study. To address this concern, the majority of the participants suggested to not include the instruction and dosage of medications in SMS reminders. This suggestion was also in line with similar findings from the patients' perception survey indicating patients' preference on receiving general SMS reminders to prevent any misunderstanding of medication regimen.

In programmatic suggestions for making the intervention fit to the Iranian context, cardiac nurses advised investigating patients' perceptions and preferences about the intervention prior to the pilot RCT. It was described to the nurses that at the same time, the patients' perception survey has been conducting and the findings from both studies would be used to refine and make the study intervention appropriate to the context. Participants also suggested that SMS reminders would be most helpful if they were sent less frequently to prevent potential dependency on or tiredness of receiving messages with high frequency. This finding is consistent with similar previous studies, too. For example, Quilici et al. (2013) examined the effect of one-month daily SMS reminders for aspirin intake (see Section 3.5.1); they reported significant improvement in medication adherence and high satisfaction among ACS patients who received the intervention. In another study, Pop-Eleches et al. (2011) examined the effect of high versus less frequent SMS reminders on adherence to ART among 431 patients in Kenya. After 48 weeks, they found that participants who received less frequent SMS reminders had significantly higher medication adherence compared to the control group ($P=0.03$). Habituation, or the reduction of a reaction to a frequent and repeated stimulus, need to be considered in sending medication reminders, particularly in long-term studies. High frequent messages might also be perceived intrusive. Considering the results from the patients' survey and nurses's focus groups, to prevent the potential fatigue or useless of receiving high frequent text messages, SMS reminders were sent once a day every morning (as patients preferred mornings and the majority of cardioprotective medications or the first dose of them are taken in the morning).

In addition to the patients' survey results, the intervention was informed by qualitative findings in which cardiac nurse professionals expressed potential effects

of the mHealth interventions, its associated challenges in the context of Iran and pragmatic suggestions to enhance the intervention design. This study revealed that Iranian cardiac nurses were open to the introduction of the mHealth intervention to improve cardiovascular medication adherence, but perceived different reasons why mHealth would be challenging to implement in the Iranian healthcare system. These involved issues of limited technology knowledge and training among patients and health care providers and lack of a shared electronic health records within Iranian health care system as well as privacy and legal issues. Nurses' views can only contribute to obtaining part of the information required to refine the intervention. Nevertheless, it is unlikely that mHealth interventions will be implemented without the vigorous support of nurses. Therefore, exploring their views was an important step. In order to develop an effective and feasible mHealth intervention, a patients' preferred design should be included (in this study, related information obtained from the patient perception survey), as it is more likely to obtain acceptability and success. The effectiveness of the automated SMS medication reminders required further piloting after making the necessary modifications (based on the findings of the study phase 1), that would inform a larger RCT.

7.1.3 Main Findings of Pilot RCT (Objectives 5–9)

Information obtained from the preclinical/ modelling phase was used to develop the context-appropriate mHealth intervention. The automated SMS medication reminder intervention was then piloted using an exploratory trial that is a critical phase of the MRC framework. It enabled the researcher to evaluate the components, acceptability and feasibility of the intervention in practice. It also provided the opportunity to determine sample size, the potential effect of the intervention (effect size), recruitment and attrition rate. In the remainder of this chapter, the effect of the automated SMS reminders on medication adherence and a number of secondary outcomes of Iranian male and female CHD patients participating in CR over the 12 weeks of the study are presented.

The Effect of the Intervention on Medication Adherence (Objective 5)

Participants in the current study were not diverse (i.e. they were homogenous) in the study variables. Based on the analytical approach used the effect of the

automated SMS reminder intervention on adherence showed promising results among Iranian CR outpatients. A Complete Case Analysis indicated positive effect of the intervention on medication adherence in the experimental group who received SMS reminders compared to those who did not. The goals of medication therapy for chronic CHD are, primarily, to prevent recurrent MI and sudden cardiac death and, secondly, to alleviate symptoms and promote quality of life (Ambrosio et al., 2016, Iqbal et al., 2015, Manolis et al., 2016, Thadani, 2016). Guideline-Directed Medical Therapy (GDMT) that promote prognosis include antiplatelet, statins, and antihypertensive agents (Piepoli et al., 2016, Yancy et al., 2016). A recent systematic review of 10 completed trials suggested that mHealth interventions can improve medication adherence in cardiovascular patients (Gandapur et al., 2016). Review studies recently showed the most successful intervention for medication adherence was text-message reminders (Santo et al., 2016, van Driel et al., 2016). These findings are consistent with the present study.

Patients in this study had inadequate self-reported medication adherence before the intervention. After 12 weeks, the intervention group that received SMS medication reminders had an improved adherence compared to the control group. These results documented that the effectiveness of SMS reminder was not only between groups but also it was effective within groups. This may illustrate the importance of medication reminder on both promoting and maintenance of adherence. Considering the WHO adherence model, for each factor in the Morisky scale that predicts medication adherence, at the end point of the study, SMS reminders showed to be effective in preventing participants' forgetfulness to take medication (patient-related dimension), reduce the frequency of nonadherence for reasons other than forgetfulness (condition-related dimension), and due to medications' side effects (therapy-related dimension). The study findings are also supported by other researchers examining the effect of text-message reminders on medication adherence in a variety of medical conditions including asthma (Strandbygaard et al., 2010), cardiovascular (Akhu-Zaheya and Wa'ed, 2016, Dale et al., 2015, Fang and Li, 2016, Pandey, 2015, Park et al., 2014, Quilici et al., 2013, Vollmer et al., 2014, Wald et al., 2014), diabetic (Arora et al., 2014), stroke (Kamal

et al., 2015) and hypertensive patients (Bobrow et al., 2016). The details of mentioned studies can be found in Chapter 3.

7.1.3.2 The Effect of the Intervention on Secondary Outcomes (Objective 6)

One of the study objectives was to explore the effect of the automated SMS reminder intervention on the secondary outcomes including Medication Adherence Self-Efficacy (MASE); Cardiac Ejection Fraction (EF); Cardiac Functional Capacity (FC); CHD-related readmission/mortality rate and Health-related Quality of Life (HR-QOL) among Iranian male and female CHD patients participating in CR after 12 weeks of the study.

This study demonstrated substantial differences between the MASE of the patients who received the automated SMS reminders and those who did not. After 12 weeks, patients in the intervention group had significantly higher self-efficacy to adhere to their medications compared to the usual care group as a result of the intervention. This finding can be understood within the theoretical context of Bandura's Self-efficacy Theory that guided the study intervention. According to Bandura (1982), self-efficacy is one of the most important factors relating to health-related behaviour change, such as medication adherence. Self-efficacy has been also considered as "cornerstone" of medication adherence (McCann et al., 2008). This concept was shown to be able to influence medication taking in patients with chronic conditions (Saffari et al., 2015). If patients have low self-efficacy in taking their medications, they are less likely to adhere to their medications (Park, 2011b). Therefore, changes in the patients' MASE may indicate the intervention effect on medication taking and the self-efficacy of the patients to follow their medication regimen (Saffari et al., 2015). Patients in this study reported low self-efficacy in taking their medications at the baseline assessment. At the end point of the study, the intervention group that received SMS medication reminders showed a significant improvement in medication adherence self-efficacy than the control group. This finding is consistent with the results from a previous systematic review that showed SMS-based interventions have the potential to promote self-efficacy through providing patients with medication reminders, as a form of social support in patients with long-term diseases (De Jongh et al., 2012). Another prospective RCT showed an improvement in the medication self-efficacy total scores over 30 days in CHD

patients who received text-message reminders; however, in contrast to the present research findings, the difference in reported improvement was not significant between the study groups (Park et al., 2015). The reason for the nonsignificant results in the Park and her colleagues' study may be due to the short follow-up period that might not be adequate to identify self-efficacy changes, specifically in the sample suffering from a chronic condition such as CHD. According to a meta review of eleven systematic reviews looking at the effect of mobile phones and SMS on promoting self-management for long-term conditions, SMS significantly improves medication adherence (Jones et al., 2014). The present study findings show that the automated SMS reminder intervention would increase self-efficacy for adherence to cardiac medications.

Adherence to cardio-protective medications and Beta Adrenergic Blockers have been shown to prevent mortality and arrhythmia, promote EF and symptoms of heart failure (Bristow, 2011). There are limited trials aimed at medication adherence that assessed CHD patients' clinical outcomes. This study demonstrated differences in cardiac functional capacity and ejection fraction (as objective measures) based upon the most recent patients' documents to capture the effect of the applied mHealth intervention on patients' clinical outcomes and address the limitation of the self-reported assessment (i.e. subjective measures). The functional capacity of patients who received the automated SMS reminders significantly improved in comparison with the usual care group. Patients who received SMS reminders also showed a significant increase in their EF over 12 weeks of the study; however, this improvement was not significant between the two study groups (intervention vs. usual care). Increased EF could be the outcome of CR programme, revascularisation treatment or/ and adherence to cardio-protective medications. The study short-term follow-up might be insufficient to capture clinical impact of such intervention. It may reflect the complexity of EF changes, as well. Similar findings were reported in a cohort study undertaken by Sueta et al. (2015) aimed at assessing post-discharge medication adherence of 402 Heart Failure (HF) patients in the United States (US). The investigators found no significant association between medication adherence and EF <50% or $\leq 40\%$ after 12 weeks indicating the complexity of medication adherence predictors. The present study showed that SMS reminders may have the potential to

serve as an effective mHealth intervention for the improvement of cardiovascular medication adherence that may consequently improve CHD patients' clinical outcomes such as functional capacity.

There were more CHD-related readmission events among the usual care group in comparison with the intervention group; however, the difference was not statistically significant between the groups. This result might be related to the short period of study and small sample size. A previous review study focused on the effect of technology-based adherence interventions on improving hospital readmission and other cardiac outcomes showed mixed results (Bosworth et al., 2011). However, a similar finding to the present study was reported in a 12-months RCT looking at the effect of mobile phone text messaging on medication adherence of hypertensive patients in South Africa (Bobrow et al., 2016). The authors found no significant differences in hospital readmissions between the study groups. The result is also consistent with another similar study, undertaken by the same researcher to the present study in Malaysia, to improve medication adherence of acute coronary syndrome patients. No difference was found in the rehospitalisation rate between the intervention and control groups after 8 weeks of the study (Khonsari et al., 2015). In the study by Choudhry et al (2013) investigating the effect of enhanced cardiovascular prescription coverage on medication adherence and rate of vascular events, the overtime differences in clinical outcomes started to deviate after 12 months. It indicates the importance of longer term follow-up to understand whether the improved adherence in the intervention group led to the improved clinical outcome.

Adherence to chronic disease management is also crucial to obtaining enhanced health outcomes and quality of life (Viswanathan et al., 2012, Kamran et al., 2014). The majority of participants had an impaired or average physical functioning and mental wellbeing prior to the study. Although there were improvements in perceived HR-QOL components in both groups at the end point of the study, the difference was not significant between the intervention and control groups. Many valid and reliable instruments are available to measure QOL. Among them, the 12-item Short Form (SF-12v2) Health Survey, a short version of the SF-36, has been shown to be a reliable and valid instrument for use among stable coronary

patients (De Smedt et al., 2013). There are limited trials to provide a clear view of the effect of mHealth interventions on CHD patients' quality of life over time. According to the result of a 6-month RCT evaluated SMS-based intervention (TEXT-MED) on low-income diabetic patients in the US, the TEXT-MED improved patients' clinical outcomes and quality of life; but the improvement was not statistically significant that is in line with the present study findings (Arora et al., 2014). It implicates no clear benefit on HR-QOL for the recipients of mHealth interventions. Among different components of CHD patients' quality of life, dimension of physical functioning had the lowest mean scores. This result is in agreement with a previous systematic review of 18 articles evaluated the quality of life in Iranian cardiovascular patients (Yaghoubi et al., 2012). The authors reasoned that this finding may be possibly related to poor quality of provided social and economical support for cardiovascular patients and expensive welfare services in Iran. Impaired QOL among CHD patients might be related to pain, anxiety, limitations in functional and social activities (Dyer et al., 2010, Xie et al., 2008). Since quality of life is multi-dimensional (i.e. physical, mental and social), it might be impossible to investigate the effect of the intervention in a short-term study with a small sample size. Therefore, a longer-term follow-up with a larger sample size are needed for a future RCT.

Participants' Characteristics and Medication Adherence (Objective 7)

Identifying factors associated with medication adherence would be useful for nurses and other health care professionals to promote their strategies (Lee et al., 2013). Five dimensions have been determined by The WHO (2003) in the Adherence Model including patient-related factors (e.g. patients' knowledge, expectations and self-efficacy) therapy-related factors (e.g. medical regimen complexity, treatment duration, side-effect), socioeconomic factors (e.g. poverty, high cost of medications, low levels of literacy, unemployment, family dysfunction), condition-related factors (e.g. severity of symptoms and disease, level of disability, co-morbidities) and health care team- and system-related factors (e.g. inadequate patient-provider relationship, lack of health insurance and poor community support). According to a systematic review of 11 studies investigating factors related to cardiovascular medication adherence, conflicting results were found (Oosterom-Calo et al., 2013). The reasons

for this could be that different studies applied diverse measures to assess adherence, which may have provided various results. Another reason could be the inclusion of patients with different characteristics in different studies (e.g. patients with different age ranges, diverse geographical regions, and different levels of disease severity). Some studies showed an association between age, sex, educational level as well as number of comorbid diseases and medication adherence (Doggrell, 2010, Fleg et al., 2011, Krueger et al., 2015, Oosterom-Calo et al., 2013). The present study, however, found no significant relationship between the patients' characteristics and medications adherence. A possible explanation might be the small sample size that caused some issues; for example, there were only a small number of elderly above 75 years old. Additionally, the majority of the participants were male (71.8%) and suffered from different comorbid conditions (82.1%). These might have an impact on identifying factors predicting medication adherence.

7.1.3.4 Patients' Perceptions of the Applied Intervention (Objective 8)

In this study, the results showed the majority of the participants in the intervention group who received SMS reminders to take their cardiovascular medications perceived the mHealth intervention positively. According to the patients' responses, reminders prevented forgetfulness in medication taking and contributed to maintain patients' interaction with healthcare system after hospital discharge, feel support, promote their independence and self-efficacy in following prescribed medication regimen. The results are in line with the principles of the Bandura's self-efficacy theory and the WHO adherence model; SMS reminders showed promise in promoting medication adherence mainly through addressing patient-related factors (i.e. forgetfulness and poor self-efficacy) and health care system-related factors (i.e. inadequate patient-provider interaction). The survey findings are also supported by studies used mobile phone SMS reminders for patients with various chronic diseases that perceived receiving medication reminders useful (Arora et al., 2014, Kamal et al., 2015, Park et al., 2014, Strandbygaard et al., 2010).

7.1.3.5 Findings to Inform Future Definitive Large-scale RCT (Objective 9)

This study showed that the MRC framework (2011) for the development and evaluation of RCTs is a helpful guideline that explains and provides support and recommendations for this particular innovation approach. The framework provided

guidance on how to develop, evaluate, and reshape a mHealth-delivered medication adherence intervention. Although there are few examples of the MRC framework application in developing mHealth-delivered interventions, the framework was successfully used in the previous studies to design technology-mediated interventions to improve medication adherence behaviour in chronic conditions (O'Carroll et al., 2010, Linn et al., 2013). According to a systematic review of 14 studies identifying the most comprehensive model to develop nursing interventions, the MRC framework were the most widely used guideline (Corry et al., 2013). In another extensive review of 21 studies conducted by Banning (2009) to examine the simple to complex adherence interventions, the MRC framework appears to be useful in the refinement and evaluation of medication adherence interventions. Application of this framework in designing interventions to improve medication intake behaviour has been also recommended by the NHS National Coordinating Centre for Service Delivery and Organisation (NCCSDO) (Horne et al., 2005). By using the MRC framework to develop and refine the intervention, resources waste is eliminated and the benefit (i.e. the proportion of adherent patients) is maximised. In addition, for interventions that are shown to be ineffective, it helps review the circular process. Then, insufficiency in the refinement or evaluation phase can be identified, rather than leaving the intervention and the process altogether (Craig et al., 2011).

Following the implementation of the patients' perception survey and qualitative focus groups (i.e. Modeling Phase), the findings had led to the refinement of the developed mHealth intervention that was fit-for-purpose to be delivered to Iranian CHD patients presented in the CR clinic. For example, focus groups indicated that mHealth-delivered medication reminders would be helpful, but it should be simple, short, easy to understand and delivered less frequently. The Modeling Phase also contributed to identifying perceptions and key preferences of Iranian CHD patients regarding the potential mHealth intervention (e.g. the timing, frequency and content of SMS reminders) and allowed the researcher to make the intervention appropriate to the Iranian context. The application of the MRC framework to develop and refine the mHealth intervention was necessary to make it fit-for-purpose and inform a larger trial (Craig et al., 2011). The automated SMS medication reminder intervention was evaluated by conducting a pilot RCT (i.e.

Exploratory Phase), in terms of recruitment, retention, acceptability and effectiveness. The results of this study illustrated positive feedback for the feasibility of recruiting participants to a mHealth study in a university-affiliated hospital in the capital city of Iran, as showed by the positive rate of the patients' recruitment. There was an approximately low attrition rate, as well. Although there was a large range in participants' age (38–84 years), the mean age of 61.8 years (Standard Deviation ± 1.02) showed the feasibility of using mHealth for older patients. A limited number of participants reported technical difficulties. There was no harm or unexpected effects on participants as a result of the study intervention.

Overall a promising evidence for the effectiveness of the automated SMS reminder intervention on cardiovascular medication adherence was provided in the two phases of the study. The main effect was observed on improved medication adherence, specifically what the intervention aimed to change. A relatively large effect (Relative Risk=2.19; 95% CI: 1.5-3.19) was found on the main outcome measure (i.e. medication adherence). High patients' satisfaction scores demonstrated the feasibility and acceptability of the SMS medication reminder intervention in an Iranian setting. Therefore, the next step is to validate the intervention effect in an adequately powered RCT. However, the present study findings added to the existing evidence supporting mHealth as an innovative approach for promoting cardiovascular medication adherence that showed to be effective, feasible and acceptable in Iran.

7.2 Strengths and Limitations

One of the study's strengths is that the MRC framework criteria (2011) were used to develop a theory- and evidence-based mHealth intervention to improve cardiovascular medication adherence that provides a comprehensive and circular process for the intervention refinement and evaluation. Moreover, Bandura's self-efficacy theory and the WHO adherence model were successfully used in the refinement of the automated SMS medication reminder intervention to overcome patient-related (i.e. forgetting and low self-efficacy) and health care system-related (i.e. poor patient-provider interaction after hospital discharge) barriers.

To the best of the researcher's knowledge, this study is one of the first studies that has used a nurse-led mHealth intervention to improve medication adherence among Iranian CHD patients. Furthermore, the intervention was refined based on the Iranian cardiac nurses' opinions and customised to CHD patients' preferences prior to its implementation. Using the tailored intervention to the local setting has made the intervention more likely to be feasible and acceptable in this particular context.

The intervention was a web-based software that was not dependent on a specific hardware. Therefore, it offered maximum portability and ease of use. It also comprised of different parts that were designed to gather and manage the patients' information and their medications, store data, schedule, send SMS and record SMS delivery status. All mentioned tasks were operated automatically. It also offered further features including query, advanced search and report generation that could be exported to a variety of standard formats.

There are some limitations to the present study that should also be noted to rule out alternative explanations. First, making fortnightly phone calls with patients in the intervention group to ensure they received the text-message reminders, may have added unintentional attention to their medication taking for this study group. The Hawthorne effect of the phone calls should be considered, although no conversation were made regarding patients' medication taking. Second, the sample for the qualitative focus groups may have underrepresented Iranian cardiac nurses as they were selected and invited through the gatekeepers to participate in the study leading to unintentional sample selection bias. However, literature suggests that the common method for selecting participants for focus groups is purposive or convenience sampling (i.e. without any random selection) who may provide the best information to answer research questions (Ritchie et al., 2013).

Third, because the sample size was small and only included CHD patients presented at an outpatient CR clinic of a university-affiliated hospital in the city of Tehran, they might not represent all Iranian CHD population. In addition, the intervention was refined and tailored to the Iranian settings. All these may limit the generalisability of the study findings. However, linking the components of the intervention to the theory or conceptual framework may be an effective way to

address the generalisability issue of the study findings and prevent duplicating attempts for further studies.

The fourth limitation of the study is the patients' self-completion bias, although the self-report questionnaire is simple, cost-efficient and the most common method of data collection (Berben et al., 2011, Osterberg and Blaschke, 2005, Rolley et al., 2008). It may be affected by recall bias and socially desirable responding (Berben et al., 2011, Rolley et al., 2008); however, a comparison of other studies demonstrated that there was an association between a patient's self-report of medication intake and blood drug levels (Glintborg et al., 2007, Ho et al., 2009, Rolley et al., 2008). There is no "gold standard" to measure the medication adherence behaviour (Ho et al., 2009, Jose and Jimmy, 2011) and all measurement approaches have their strengths and limitations (Jose and Jimmy, 2011, Rolley et al., 2008). For example, application of direct methods such as detection of a metabolite or marker in a blood sample as well as electronic monitoring device or Medication Event Monitoring System (MEMS) may overcome the limitation of self-report methods; however, they are expensive and less practical particularly in a developing country such as Iran (Jose and Jimmy, 2011, Park et al., 2014). Considering the anxiety that CHD patients may experience following the cardiac event and hospital discharge, using MEMS may cause additional levels of stress in these patients (Park et al., 2014). Moreover, to the researcher's knowledge, electronic monitoring devices for medication taking were not available in Iran during the study time. There was also no electronic pharmacy claim data in this country to monitor the prescription refill or measuring adherence using Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC). Pill count method may not be a fully reliable method because the patients in order to appear adherent can change medications between bottles or throw them out before the follow-up visit (Jose and Jimmy, 2011). Therefore, a combination of different measures was used in this study to maximise the accuracy of adherence assessment. In this study, the NYHA classification (with an adequate validity and reliability in measuring functional status) was used to measure cardiac function capacity of the participants that the subjectivity issue is a common critique of this measure. To increase the objectivity of the NYHA classifications, objective assessment were conducted by cardiologists (who were unaware of the patient allocation) at the

baseline and endpoint of the study. The objective assessment were made based on the results of electrocardiograms, stress tests, x-rays and echocardiograms (see Section 5.3).

Fifth, the follow up period of 12 weeks was relatively short and did not provide long-term sustainability of the intervention effect on adherence or clinical outcomes, considering the setting of a chronic disease such as CHD, in particular. However, the study evaluated the effect of the mHealth intervention on improving cardiovascular medication adherence during the early phase of hospital discharge when the majority of CHD patients are most susceptible of discontinuation of their medications (Airoldi et al., 2007, Balaguer-Malfagón et al., 2006, Park et al., 2014). In this study, the number of patients who dropped out from the CR programme was not measured as this was beyond the scope of the present study. However, there might be a potential association between the CR drop outs and medication adherence that needs to be explored in further studies.

7.3 Implications of the Study

The MRC framework was applied to determine the feasibility and refinement of the nurse-led mHealth intervention to improve cardiovascular medication adherence based on the principles of the self-efficacy theory and the WHO medication adherence model. According to the study findings, the effectiveness of the intervention was found to be statistically significant at least in the short term in achieving an improvement in reported levels of adherence to cardioprotective medications.

This two-phase study has established feasibility and acceptability with a nurse-led mHealth intervention among CHD patients in Iran. It will also inform a future definitive RCT in order to confirm the present study findings and validate the mHealth intervention as a potential solution to the medication nonadherence challenges. The following sections will discuss the potential implications of the present research at different levels of healthcare, micro- (patients and providers), meso- (healthcare organisation) and macro-level (health policy).

7.3.1 Implications at Micro-level (Patients and Providers)

According to the WHO adherence model, patient-level factors refer to patients' characteristics such as knowledge, beliefs and self-efficacy that only comprise the small proportion of the variability in nonadherence. The quality of communication between the health care providers and patients has been found to have an important impact on adherence to the recommended treatment and consequently on patients' clinical outcomes (Berben et al., 2012, Najafi et al., 2016, Zolfaghari et al., 2012). Healthcare professionals providing care for patients with cardiovascular disease are strongly encouraged to employ adherence supporting interventions in their every day practice (Berben et al., 2011). As the most influential person in improving the patients' adherence to therapeutic regimen, nurses and health care providers should be aware of the potential effects of innovative contemporary approaches at multiple levels, the micro-, meso-, and macro-level (Berben et al., 2011, McLeroy et al., 1988). They can significantly contribute to provide the patients with support and help them improve self-efficacy in medication adherence that can lead to a better patients' adaptation with their treatment regimen in the post-discharge period (Najafi et al., 2016). In this way, nurses' optimal selection of the myriad of interventions available is of great importance; it can lead to patients' adherence to prescribed medications and prevent progression of the negative outcomes, and the disease-related complications (Gandhi et al., 2016, Stolic et al., 2010).

As a part of electronic health, telenursing is an encouraging approach that can expand the involvement of nurses in patient care (Souza-Junior et al., 2016). It also provided the possibility of delivering nursing care through information and communication technology including the Internet, and mobile phones among which mobile phone is widely available and used by most of the people (Kumar, 2011). Without the active support of nurses, the implementation of mobile health interventions to achieve the optimal level of care is less possible (Zolfaghari et al., 2012). Application of mHealth and specifically text-messaging have been found to be efficient and promising to deliver nurse-led interventions that manage various chronic diseases (Jones et al., 2014). Furthermore, it can provide patients with medication reminder and post-discharge follow-up, that potentially strengthens the patient-provider interaction (Akhu-Zaheya and Wa'ed, 2016, Tsiantou et al., 2010).

According to the WHO, innovative care for chronic patients has been recommended (Duplaga and Winnem, 2006) and it indicates that quality care should be delivered to patients whenever is required through different approaches, not limited to traditional face-to-face visits. Hence, the health care providers are responsible for providing patients' access to care using mobile phones or other means of communication in addition to clinical visits (Gentles et al., 2010).

During hospitalisation, nurses are responsible for administering patients' medications regularly based on the hospital's policy; however, non-adherence occurs as a major problem among CHD patients during the early phase of hospital discharge (Akhu-Zaheya and Wa'ed, 2016). In Iran, after patients' discharge from the hospital, a follow-up home visit is barely available and patients' drop-out from a hospital-based CR is quite high (Heydarpour et al., 2015, Moradi et al., 2011). Thus, mobile phone text messaging could be an accessible means of support to promote patients' post-discharge follow-up (Gandapur et al., 2016, Sarabi et al., 2016, Thakkar et al., 2015). This study evaluated one of the telenursing approaches (i.e. mobile phone text-messaging) and showed the significant effect of using automated SMS reminders on promoting adherence to the prescribed regimen of medication among adult patients with CHD. Considering the shortage of nurses in developing countries such as Iran, it was found in the present study that automated text-messaging as a type of mHealth interventions has the potential to be used as an alternative to in-person appointments in order to improve post-discharge medication adherence.

7.3.2 Implications at Meso-level (Healthcare Organisation)

The delivery and the quality of the services offered are coordinated and evaluated by the health care organisation (Berben et al., 2012, McLeroy et al., 1988). Interventions used in regular clinical practice to optimise patients' medication adherence can illustrate the characteristics or practice patterns of hospitals, which play their roles under meso-level factors (Berben et al., 2012). Although health promotion and prevention programmes should be essential components of health care organisations, this is far from daily clinical practice (Rogers et al., 2015, World Health Organisation, 2002). It is necessary for healthcare organisations to expose their employees to specialised knowledge and skills available for chronic care

management along with training on acute care and provide them with innovative evidence-based tools and techniques that promote therapeutic management by assisting patients with adherence and other self-management approaches (Dwarswaard et al., 2016).

Application of electronic health is essential for organised, integrated, and evidence-informed patient care (Sharifi et al., 2013). Moreover, it is useful to review health trends and clinical care process (Souza-Junior et al., 2016). In terms of chronic care management including cardiovascular diseases, technology-mediated interventions such as text-messaging can provide patients with a reminder with different components, and it can help encourage patient's self-efficacy and modify health behaviours such as adherence to medication regimens or other important health changes when they are away from hospital (Gandapur et al., 2016, Sarabi et al., 2016, Thakkar et al., 2015).

It was shown in different review studies that mHealth-delivered interventions such as mobile phone text-messaging as a means of communication has a potential for use in healthcare system to improve clinical outcomes and behavior modifications (Gandhi et al., 2016, Sarabi et al., 2016, Thakkar et al., 2015, Albertini et al., 2011). In the present study, the mHealth intervention of automated SMS medication reminders showed a significant improvement in patients' adherence. Unlike complicated interventions and time-consuming face-to-face approaches, SMS reminders are transmitted automatically to patients beyond a specific location at a predefined time with limited efforts from health care professionals. It was also designed to provide a database for patient information management in an efficient and organised way that enable users to query, advance search, generate reports and export to different formats.

7.3.3 Implications at Macro-level (Health Policy)

Based on the study findings and from what has been discussed previously, mHealth has excellent potential to be widely used in the future as it could be helpful in improving efficiency and effectiveness of healthcare delivery and patients' follow-up in medical sectors. Despite the advantages of mHealth applications such as improved patient access to health care, reduced unnecessary face-to-face visits and

eliminated total health care expenses, mHealth interventions have been less developed in comparison with other approaches (Sharifi et al., 2013) due to a variety of challenges highlighted by cardiac nurses in this study. Lack of IT knowledge and training, legal ambiguities, privacy and security concerns and educational issues have been identified as challenges of implementation of mHealth in Iran that deserve and require policymakers' attention.

The effectiveness of mHealth interventions has important implications for future health policy and the development of strategies related to medication adherence and secondary prevention of cardiovascular disease. This is particularly of importance when considering the adherence rate was reported to be 38.8-60.0% for cardiovascular medications (Sarayani et al., 2013). In Iran, nonadherence to medications was found to be the leading cause of ischemic heart disease rehospitalisation followed by a high level of stress and physical inactivity (Heydari et al., 2015). The importance of preventative policies and innovative interventions (e.g. mHealth) which focus on improving adherence to therapeutic regimen among cardiac patients has been highlighted in different studies (Dabaghian et al., 2016, Heydari et al., 2015, Sarayani et al., 2013). The findings of the present study would suggest that development of theory-based mHealth interventions that tailored to the local context and exploring their effectiveness on medication adherence are areas pertinent for future policy and secondary prevention improvement in Iran. The study also demonstrated that the significant improvement in medication adherence may be achievable through the implementation of the mHealth intervention for CHD patients.

7.4 Conclusion

Qualitative and quantitative data collected during refinement and piloting of the automated SMS medication reminders suggested that the nurse-led mHealth intervention in the Iranian CHD patients participated in CR programme had the desired effect (improved cardiovascular medication adherence) and confirmed that the recruitment and data collection strategies used were feasible for implementation in a future definitive RCT. According to the MRC framework (2013), the next step will be to assess the intervention cost-effectiveness and to validate the present study

results by conducting a larger trial in order to confirm the feasibility and transferability of the intervention from research into practice. The large-scale RCT is the Evaluation Phase of the MRC framework (Senn et al., 2013).

7.4.1 What was already known?

- Poor medication adherence is one of the most significant barriers to successful treatment among CHD patients after discharge from the hospital that could be related to unintentional reasons such as forgetfulness and inadequate self-efficacy in medication taking.
- Mobile phone text messaging was evaluated in different chronic conditions, and shown to be effective in optimising adherence and health outcomes; however, few studies developed, refined and evaluated a theory-based mHealth intervention based on the MRC framework to promote medication adherence among CHD patients in an Iranian CR setting.
- In Iran, there are limited follow-up home visits available after discharge from a cardiac event and regular attendance in an outpatient cardiac rehabilitation programme is suboptimal. Therefore, telenursing using SMS could be the most accessible way to potentially promote patients' adherence to prescribed medication regimen and self-efficacy.

7.4.2 What this study has added to the body of knowledge?

Conducting a multi-stage mixed methods research study using the MRC framework contributed to collect and analyse rich research data. The original literature highlighted the lack of research which developed and evaluated a theory-based, patient-centered, nurse-led mHealth intervention to improve cardiovascular medication adherence in the Iranian CR setting. In addition, the most recent literature identified the need to explore perspectives of both CHD patients and experienced cardiac nurses about potential effects and challenges of mHealth implementation in Iran. The aims of the study addressed these issues. The MRC framework was used as a guide to develop and evaluate the study mHealth intervention. The findings supported the application of behavioural theory to practice, in this case self-efficacy construct. The automated SMS medication reminder was developed based on the dimensions of adherence suggested by the

WHO and Bandura' Self-efficacy Theory. The intervention was refined according to the findings from Phase 1 and then piloted in an Iranian CR setting. A self-completed survey of CHD patients and cardiac nurses' focus groups were conducted as part of the preclinical/ modelling phase which informed the second phase of the study (exploratory trial). The survey results indicated that mobile phone ownership and the use of text messages were relatively high among Iranian CHD patients and using mHealth intervention to improve medication adherence for this group of patients would be acceptable. Focus groups findings revealed that Iranian cardiac nurses were open to the introduction of the mHealth intervention to improve medication adherence, but perceived different reasons why mHealth would be challenging to implement in the Iranian healthcare system. The nurses also discussed their views and recommendations about the refinement of the mHealth intervention. In the second phase of the study, the refined mHealth intervention was piloted among 78 Iranian CR patients for 12 weeks. The findings showed that a nurse-led mHealth intervention was well accepted and feasible with significantly higher reporting of medication adherence in Iranian CHD patients at 3 months. In order to identify the long-term impact of the mHealth intervention on medication adherence, a larger study with longer follow-up is needed.

In summary:

- This study provides a full description of the refinement and evaluation of a nurse-led mHealth intervention to promote cardiovascular medication adherence in Iran, using the WHO adherence model and the self-efficacy theory principles, based upon the MRC framework to inform a future definitive RCT.
- The processes followed to develop the automated SMS medication reminder intervention can be replicated in other studies. The evaluation of qualitative and quantitative data improved and tailored the intervention to the local context and ensured it could be applied to the Iranian CHD patients.
- Automated SMS-based intervention as reminders showed promise in encouraging CHD patients to adhere to the prescribed medication regimen and improving self-efficacy in medication taking.

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APPENDICES

Appendix 1: CONSORT Checklist



CONSORT-EHEALTH checklist (V.1.6.1): Information to include when reporting ehealth/mhealth trials (web-based/Internet-based intervention and decision aids, but also social media, serious games, DVDs, mobile applications, certain telehealth applications)

Do you feel items are missing/unclear/unnecessary? Please comment at <http://tinyurl.com/consort-ehealth-v1-5>

If you are working on a manuscript submission, please fill in this checklist electronically at <http://tinyurl.com/consort-ehealth-v1-6>

Section/Topic	Item No.	CONSORT* Checklist Item	EHEALTH Extensions (additions to, or clarification of the CONSORT item)	Importance
TITLE & ABSTRACT	1a	Identification as a randomized trial in the title	<p>i) Identify the mode of delivery in the title. Preferably use "web-based" and/or "mobile" and/or "electronic game" in the title. Avoid ambiguous terms like "online", "virtual", "interactive". Use "Internet-based" only if Intervention includes non-web-based Internet components (e.g., email), use "computer-based" or "electronic" only if offline products are used. Use "virtual" only in the context of "virtual reality" (3-D worlds). Use "online" only in the context of "online support groups". Complement or substitute product names with broader terms for the class of products (such as "mobile" or "smart phone" instead of "iphone"), especially if the application runs on different platforms.</p> <p>ii) Mention non-web-based components or important co-interventions in the title, if any (e.g., "with telephone support").</p> <p>iii) Mention primary condition or target group in the title, if any (e.g., "for children with Type I Diabetes") Example: <i>A Web-based and Mobile Intervention with Telephone Support for Children with Type I Diabetes: Randomized Controlled Trial</i></p>	<p>Essential</p> <p>Highly Recommended</p> <p>Essential</p>
	1b	Structured summary of trial design, methods, results, and conclusions NPT** extension: Description of experimental treatment,	<p>Methods (in Abstract):</p> <p>i) Mention key features/functionality/components of the intervention and comparator in the abstract. If possible, also mention theories and principles used for designing the site. Keep in mind the needs of systematic reviewers and indexers by including important synonyms.</p>	Essential

		comparator, care providers, centers, and blinding status	(Note: Only report in the abstract what the main paper is reporting. If this information is missing from the main body of text, consider adding it)	
			ii) Clarify the level of human involvement in the abstract , e.g., use phrases like “fully automated” vs. “therapist/nurse/care provider/physician-assisted” (mention number and expertise of providers involved, if any). (Note: Only report in the abstract what the main paper is reporting. If this information is missing from the main body of text, consider adding it)	Highly Recommended
			iii) Open vs. closed, web-based (self-assessment) vs. face-to-face assessments in abstract: Mention how participants were recruited (online vs. offline), e.g., from an open access website or from a clinic or a closed online user group (closed usergroup trial), and clarify if this was a purely web-based trial, or there were face-to-face components (as part of the intervention or for assessment). Clearly say if outcomes were <i>self-assessed</i> through questionnaires (as common in web-based trials). Note: In traditional offline trials, an open trial (open-label trial) is a type of clinical trial in which both the researchers and participants know which treatment is being administered. To avoid confusion, use “blinded” or “unblinded” to indicated the level of blinding instead of “open”, as “open” in web-based trials usually refers to “open access” (i.e. participants can self-enrol) (Note: Only report in the abstract what the main paper is reporting. If this information is missing from the main body of text, consider adding it)	Highly Recommended
			iv) Results in abstract must contain use data: Report number of participants enrolled/assessed in each group, the <i>use/uptake</i> of the intervention (e.g., attrition/adherence metrics, use over time, number of logins etc.), in addition to primary/secondary outcomes. (Note: Only report in the abstract what the main paper is reporting. If this information is missing from the main body of text, consider adding it)	Highly recommended
			v) Conclusions/Discussions in abstract for negative trials: Discuss the primary outcome - if the trial is negative (primary outcome not changed), and the intervention was not used, discuss whether negative results are attributable to lack of uptake and discuss reasons.	Highly Recommended
INTRODUCTION	2a	Scientific background and explanation of rationale	i) Describe the problem and the type of system/solution that is object of the study: intended as stand-alone intervention vs. incorporated in broader health care program? [1] Intended for a particular patient population? [1] Goals of the intervention, e.g., being more cost-effective to other interventions [1], replace or complement other solutions? (Note: Details about the intervention are provided in “Methods” under 5)	Essential
			ii) Scientific background, rationale: What is known about the (type of) system that is the object of the study (be sure to discuss the use of similar systems for other conditions/diagnoses, if appropriate), motivation for the study, i.e., what are the reasons for and what is the context for this specific study, from which stakeholder viewpoint is the study performed, potential impact of findings [2]. Briefly justify the choice of the comparator.	Essential
	2b	Specific objectives or hypotheses	<i>No EHEALTH-specific additions here</i> (note: Contrary to STARE-HI we do not recommend to mention IRB approval in this section - JMIR and other journals typically recommend this as a subheading under “methods”. CONSORT-EHEALTH has a separate item for ethical considerations)	
METHODS	3a	Trial design	<i>No EHEALTH-specific additions here</i>	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	i) Bug fixes, Downtimes, Content Changes: <i>ehealth systems are often dynamic systems. A description of changes to methods therefore also includes important changes made on the intervention or comparator during the trial (e.g., major bug fixes or changes in the functionality or content) (5-iii) and other “unexpected events” that may have influenced study design</i>	Highly Recommended

such as staff changes, system failures/downtimes, etc. [2].

Participants	4a	Eligibility criteria for participants	i) Computer / Internet literacy is often an implicit “de facto” eligibility criterion - this should be explicitly clarified [1].	Highly Recommended
			ii) Open vs. closed, web-based vs. face-to-face assessments: Mention how participants were recruited (online vs. offline), e.g., from an open access website or from a clinic, and clarify if this was a purely web-based trial, or there were face-to-face components (as part of the intervention or for assessment), i.e., to what degree the study team got to know the participant. In online-only trials, clarify if participants were quasi-anonymous and whether having multiple identities was possible or whether technical or logistical measures (e.g., cookies, email confirmation, phone calls) were used to detect/prevent these.	Essential
			iii) Information given during recruitment. Specify how participants were briefed for recruitment and in the informed consent procedures (e.g., publish the informed consent documentation as appendix, see also item X26), as this information may have an effect on user self-selection, user expectation and may also bias results.	Highly Recommended
	4b	Settings and locations where the data were collected	i) Clearly report if outcomes were (self-)assessed through online questionnaires (as common in web-based trials) or otherwise.	Essential
			ii) Report how institutional affiliations are displayed to potential participants [on ehealth media], as affiliations with prestigious hospitals or universities may affect volunteer rates, use, and reactions with regards to an intervention” [1]. (Not a required item – describe only if this may bias results)	Recommended
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually	i) Mention names, credential, affiliations of the developers, sponsors, and owners [6] (if authors/evaluators are owners or developer of the software, this needs to be declared in a “Conflict of interest” section or mentioned elsewhere in the manuscript).	Highly Recommended
administered			ii) Describe the history/development process of the application and previous formative evaluations (e.g., focus groups, usability testing), as these will have an impact on adoption/use rates and help with interpreting results.	Highly Recommended
			iii) Revisions and updating. Clearly mention the date and/or version number of the application/intervention (and comparator, if applicable) evaluated, or describe whether the intervention underwent major changes during the evaluation process, or whether the development and/or content was “frozen” during the trial. Describe dynamic components such as news feeds or changing content which may have an impact on the replicability of the intervention (for unexpected events see item 3b).	Highly Recommended
			iv) Provide information on quality assurance methods to ensure accuracy and quality of information provided [1], if applicable.	Highly Recommended
			v) Ensure replicability by publishing the source code, and/or providing screenshots/screen-capture video, and/or providing flowcharts of the algorithms used. Replicability (i.e., other researchers should in principle be able to replicate the study) is a hallmark of scientific reporting.	Highly Recommended
			vi) Digital preservation: Provide the URL of the application, but as the intervention is likely to change or disappear over the course of the years; also make sure the intervention is archived (Internet Archive, webcitation.org, and/or publishing the source code or screenshots/videos alongside the article). As pages behind login screens cannot be archived, consider creating demo pages which are accessible without login.	Highly Recommended
			vii) Access: Describe how participants accessed the application, in what setting/context, if they had to pay (or were paid) or not, whether they had to be a member of specific group. If known, describe how participants obtained “access to the platform and Internet” [1]. To ensure access for editors/reviewers/readers, consider to provide a “backdoor” login account or demo mode for reviewers/readers to explore the application (also important for archiving purposes, see vi).	Essential

		viii) Describe mode of delivery, features/functionalities/components of the intervention and comparator, and the theoretical framework [6] used to design them (instructional strategy [1], behaviour change techniques, persuasive features, etc., see e.g., [7, 8] for terminology). This includes an in-depth description of the content (including where it is coming from and who developed it) [1], “whether [and how] it is tailored to individual circumstances and allows users to track their progress and receive feedback” [6]. This also includes a description of communication delivery channels and – if computer-mediated communication is a component – whether communication was synchronous or asynchronous [6]. It also includes information on presentation strategies [1], including page design principles, average amount of text on pages, presence of hyperlinks to other resources etc. [1].	Essential	
		ix) Describe use parameters (e.g., intended “doses” and optimal timing for use) [1]. Clarify what instructions or recommendations were given to the user, e.g., regarding timing, frequency, heaviness of use [1], if any, or was the intervention used ad libitum.	Highly Recommended	
		x) Clarify the level of human involvement (care providers or health professionals, also technical assistance) in the e-intervention or as co-intervention. Detail number and expertise of professionals involved, if any, as well as “type of assistance offered, the timing and frequency of the support, how it is initiated, and the medium by which the assistance is delivered” [6]. It may be necessary to distinguish between the level of human involvement required for the trial, and the level of human involvement required for a routine application outside of a RCT setting (discuss under item 21 – generalizability).	Highly recommended	
		xi) Report any prompts/reminders used: Clarify if there were prompts (letters, emails, phone calls, SMS) to use the application, what triggered them, frequency, etc. [1]. It may be necessary to distinguish between the level of prompts/reminders required for the trial, and the level of prompts/reminders for a routine application outside of a RCT setting (discuss under item 21 – generalizability).	Essential	
		xii) Describe any co-interventions (incl. training/support): Clearly state any “interventions that are provided in addition to the targeted eHealth intervention” [1], as ehealth intervention may not be designed as stand-alone intervention. This includes training sessions and support [1]. It may be necessary to distinguish between the level of training required for the trial, and the level of training for a routine application outside of a RCT setting (discuss under item 21 – generalizability).	Essential	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	<p>i) If outcomes were obtained through online questionnaires, describe if they were validated for online use [6] and apply CHERRIES items to describe how the questionnaires were designed/deployed [9].</p> <p>ii) Describe whether and how “use” (including intensity of use/dosage) was defined/measured/monitored (logins, logfile analysis, etc.). Use/adoption metrics are important process outcomes that should be reported in any ehealth trial.</p> <p>iii) Describe whether, how, and when qualitative feedback was obtained from participants (e.g., through emails, feedback forms, interviews, focus groups).</p>	Highly Recommended
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No EHEALTH-specific additions here	
Sample size	7a	How sample size was determined NPT: When applicable, details of whether and how the clustering by care provides or centers was addressed	i) Describe whether and how expected attrition was taken into account when calculating the sample size	Highly Recommended
	7b	When applicable, explanation of any interim analyses and stopping guidelines	No EHEALTH-specific additions here	
Randomisation:				

Sequence generation	8a	Method used to generate the random allocation sequence NPT: When applicable, how care providers were allocated to each trial group	<i>No EHEALTH-specific additions here</i>	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	<i>No EHEALTH-specific additions here</i>	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	<i>No EHEALTH-specific additions here</i>	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	<i>No EHEALTH-specific additions here</i>	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how NPT: Whether or not administering co-interventions were blinded to group assignment	<p>i) Specify who was blinded, and who wasn't. Usually, in web-based trials it is not possible to blind the participants [1, 3] (this should be clearly acknowledged), but it may be possible to blind outcome assessors, those doing data analysis or those administering co-interventions (if any).</p> <p>ii) Informed consent procedures (4a-ii) can create biases and certain expectations - discuss e.g., whether participants knew which intervention was the "intervention of interest" and which one was the "comparator".</p>	Essential Highly Recommended
	11b	If relevant, description of the similarity of interventions	<i>(this item is usually not relevant for ehealth trials as it refers to similarity of a placebo or sham intervention to a active medication/intervention)</i>	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes NPT: When applicable, details of whether and how the clustering by care providers or centers was addressed	<i>i) Imputation techniques to deal with attrition / missing values: Not all participants will use the intervention/comparator as intended and attrition is typically high in ehealth trials. Specify how participants who did not use the application or dropped out from the trial were treated in the statistical analysis (a complete case analysis is strongly discouraged, and simple imputation techniques such as LOCF may also be problematic [4]).</i>	Essential
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	<i>No EHEALTH-specific additions here</i>	
Ethics & Informed Consent	X26	<i>(not a CONSORT item)</i>	<p>i) Comment on ethics committee approval.</p> <p>ii) Outline informed consent procedures e.g., if consent was obtained offline or online (how? Checkbox, etc.?), and what information was provided (see 4a-ii). See [6] for some items to be included in informed consent documents.</p> <p>iii) Safety and security procedures, incl. privacy considerations, and "any steps taken to reduce the likelihood or detection of harm (e.g., education and training, availability of a hotline)" [1].</p>	Highly Recommended Highly Recommended Highly Recommended
RESULTS Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome NPT: The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider in each center	<i>No EHEALTH-specific additions here</i>	

	13b	For each group, losses and exclusions after randomisation, together with reasons	i) Strongly recommended: An attrition diagram (e.g., proportion of participants still logging in or using the intervention/comparator in each group plotted over time, similar to a survival curve) [5] or other figures or tables demonstrating usage/dose/engagement.	<i>Highly Recommended</i>
Recruitment	14a	Dates defining the periods of recruitment and follow-up	i) Indicate if critical "secular events" [1] fell into the study period , e.g., significant changes in Internet resources available or "changes in computer hardware or Internet delivery resources" [1]. <i>No EHEALTH-specific additions here</i>	<i>Highly Recommended</i>
	14b	Why the trial ended or was stopped [early]		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group NPT: When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group	i) In ehealth trials it is particularly important to report demographics associated with digital divide issues , such as age, education, gender, social-economic status, computer/Internet/ehealth literacy of the participants, if known.	<i>Essential</i>
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	i) Report multiple "denominators" and provide definitions: Report N's (and effect sizes) "across a range of study participation [and use] thresholds" [1], e.g., N exposed, N consented, N used more than x times, N used more than y weeks, N participants "used" the intervention/comparator at specific pre-defined time points of interest (in absolute and relative numbers per group). Always clearly define "use" of the intervention. ii) Primary analysis should be intent-to-treat; secondary analyses could include comparing only "users", with the appropriate caveats that this is no longer a randomized sample (see 18-i).	<i>Essential</i> <i>Highly Recommended</i>
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	i) In addition to primary/secondary (clinical) outcomes, the presentation of process outcomes such as metrics of use and intensity of use (dose, exposure) and their operational definitions is critical. This does not only refer to metrics of attrition (13-b) (often a binary variable), but also to more continuous exposure metrics such as "average session length". These must be accompanied by a technical description how a metric like a "session" is defined (e.g., timeout after idle time) [1] (report under item 6a). <i>No EHEALTH-specific additions here</i>	<i>Highly Recommended</i>
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	i) A subgroup analysis of comparing only users is not uncommon in ehealth trials, but if done it must be stressed that this is a self-selected sample and no longer an unbiased sample from a randomized trial (see 16-iii).	<i>Highly Recommended</i>
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	i) Include privacy breaches, technical problems. This does not only include physical "harm" to participants, but also incidents such as perceived or real privacy breaches [1], technical problems, and other unexpected/unintended incidents. "Unintended effects" also includes unintended <i>positive</i> effects [2]. ii) Include qualitative feedback from participants or observations from staff/researchers , if available, on strengths and shortcomings of the application, especially if they point to unintended/unexpected effects or uses. This includes (if available) reasons for why people did or did not use the application as intended by the developers.	<i>Highly Recommended</i> <i>Highly Recommended</i>
Interpretation/ Principal Findings	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence NPT: In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	i) Restate study questions and summarize the answers suggested by the data [2], starting with primary outcomes and process outcomes (use). ii) Highlight unanswered new questions, suggest future research [2].	<i>Essential</i> <i>Highly Recommended</i>

DISCUSSION Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	i) Typical limitations in ehealth trials: Participants in ehealth trials are rarely blinded. Ehealth trials often look at a multiplicity of outcomes, increasing risk for a Type I error. Discuss biases due to non-use of the intervention/usability issues, biases through informed consent procedures, unexpected events.	<i>Essential</i>
Generalisability	21	Generalisability (external validity, applicability) of the trial findings NPT: External validity of the trial findings according to the intervention, comparators, patients, and care providers or centers involved in the trial	i) Generalizability to other populations: In particular, discuss generalizability to a general <i>Internet</i> population, outside of a RCT setting, and general patient population, including applicability of the study results for other organizations [2]. ii) Discuss if there were elements in the RCT that would be different in a routine application setting (e.g., prompts/reminders, more human involvement, training sessions or other co-interventions) and what impact the omission of these elements could have on use, adoption, or outcomes if the intervention is applied outside of a RCT setting.	<i>Highly Recommended</i> <i>Highly Recommended</i>

OTHER INFORMATION

Registration	23	Registration number and name of trial registry	<i>No EHEALTH-specific additions here</i>	
Protocol	24	Where the full trial protocol can be accessed, if available	<i>No EHEALTH-specific additions here</i>	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	<i>No EHEALTH-specific additions here</i>	
Competing interests	X27 <i>(not a CONSORT item)</i>		i) In addition to the usual declaration of interests (financial or otherwise), also state the "relation of the study team towards the system being evaluated" [2], i.e., state if the authors/evaluators are distinct from or identical with the developers/sponsors of the intervention.	<i>Highly Recommended</i>

* CONSORT = Consolidated Standards of Reporting Trials [10]

** NPT = non pharmacological treatment (CONSORT extension) [11]

Appendix 2: Review of mHealth Studies

Study	mHealth	Target Population	Control group	Described measures	Adherence outcome	Other outcomes
(Strandbygaard et al., 2010)	12 weeks daily TM reminder for anti-asthmatic medication	Subjects aged 18–45 years, with a clinical history of asthma and a positive Methacholine challenge test (n=26)	Control group received no TM reminder	1. Medicine count and pharmacy reports, 2. Reimbursement of asthma medication, and change in exhaled nitric oxide levels, lung function, and airway responsiveness at the start of the study and week 4 and week 12	Improvement in the mean adherence rate of the SMS group whereas the mean adherence rate in the control group decreased.	No significant differences
(Zolfaghari et al., 2012)	3 months SMS and telephone follow-up on type 2 diabetes adherence (twice a week for the 1st month and every week for the 2nd and 3rd month.)	Patients with type 2 diabetes (n=77)	2 groups: telephone follow-up only (n=39); and SMS only (n=38)	Glycosylated haemoglobin HbA1c value and the Self-reported adherence questionnaire related to adherence therapeutic regimen at the beginning of the study and after 3 and 6 months	Physical exercise, diabetic medication taking and diet adherence improved at post-test compared with that at pretest. There was no significant difference in adherence in two groups.	Significant change in HbA1c for the SMS group, as post-test; Significant percentage change in HbA1c for the tel group. No significant difference between 2 interventions (p=0.186).
(Quilici et al., 2013)	1 month daily personalised SMS reminder for aspirin intake, with different formulation every day	Patients undergone coronary stenting for ACS (n=250)	Standard care group (n=249)	One month self-reported aspirin adherence and + controlled aspirin adherence using platelet function testing	Improved adherence as reported by patients, OR [95% CI]: 0.37 [0.15–0.90]; P = 0.02 and as shown by platelet testing, 0.43 [0.22–0.86]; P=0.01	N/A

Study	mHealth	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
(Arora et al., 2014)	2 daily unidirectional TM for 6 months within the framework of the Health Belief Model	Patients with poorly controlled diabetes (n=128)	control group received no TM	1. Change in Hb A1C level, 2. Morisky Medication Adherence Scale, self-efficacy, performance of self-care tasks, quality of life, diabetes-specific knowledge, emergency department utilisation, and patient satisfaction.	Self-reported medication adherence improved from 4.5 to 5.4 in the TM group compared with a net decrease of -0.1 in the controls.	No significant improvement in Hb A1C. It decreased by 1.05% in the TM group compared with 0.60% in the controls. Decreased emergency utilisation. 93.6% were satisfied and 100% would recommend it.
(Park et al., 2014)	1. TM for medication reminders and education, 2. Educational TM only, 3. No TM (30 days)	patients with CHD (n=90)	Control group received no TM.	1. to compare medication adherence among 3 groups (MEMS), self-reported adherence (MMAS) 2. to explore feasibility and patient satisfaction with TM	TM patients had higher percentage of correct doses taken (P=0.02), taken on schedule (P=0.01), percentage number of doses (P=0.01)	Both experimental groups reported high satisfaction with receiving TM.
(Vollmer et al., 2014)	1. Regular: automated calls 2. Enhanced: reminder letters, Electronic Medical Record feedback and mailed materials	40 years or older, had diabetes mellitus or atherosclerotic cardiovascular disease, and suboptimal adherent (n= 21752)	Usual Care (UC) received no intervention	1. Medication adherence; 2. BP and lipid levels Modified version of (PDC) Electronic Medical Record: healthcare utilisation, CVD, BP and lipid levels	Both interventions significantly increased adherence compared with UC.	Statin users, enhanced group had significantly lower LDL at follow-up compared with UC ($\Delta=-1.5$; 95% CI, -2.7 to -0.2 mg/ dL)

Study	mHealth	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
(Wald et al., 2014)	TM for medication reminders: daily for 2 weeks, alternate days for 2 weeks and weekly thereafter for 22 weeks	Patients taking BP and/or lipid-lowering medications (n=303)	Control group received no TM.	1. Medication use at 6 months, exceeding 80% of the prescribed regimen. Determined by personal enquiry, or using general practice e-records. 2. BP and serum cholesterol at randomisation	Lower non-adherence rates among TM group 14/150 (9%) vs. control 38/151 (25%) (95% CI: 7–24), P=0.001.	No significant differences in BP and LDL cholesterol between groups
(Dale et al., 2015)	Personalised 24-week automated daily SMS and a supporting website based on social cognitive theory (n=61)	Adults diagnosed with CHD (n=123)	Centre-based CR received no intervention (n=62)	1. Adherence to healthy lifestyle behaviours: self-reported composite health behaviour score (≥ 3) at 3, 6 months 2. Medication adherence score, self-efficacy, illness perceptions, and anxiety and/or depression at 6 months.	The intervention group reported significantly greater medication adherence score (mean difference: 0.58, 95% CI 0.19–0.97; P=0.004).	Significant effect in the intervention for the primary outcome at 3 months (AOR 2.55, 95% CI 1.12–5.84; P=0.03), but not at 6 months (AOR 1.93, 95% CI 0.83–4.53; P=0.13)
(Kamal et al., 2015)	2 months daily SMS reminder contained medication reminder(s) + Twice weekly health information using the Health Belief Model and Social Cognitive theory	Adult stroke patients on multiple medications with access to a cell phone (n=200)	Control group received no SMS.	1. Self-reported medication adherence (MMAS) 2. BP: measured via Mindray Datascope Equator at registration visit and after interview with the participant sitting and relaxed.	After 2 months, the mean medication score was 7.4 (95% CI: 7.2–7.6) in the intervention while 6.7 (95% CI: 6.4–7.02) in the control group.	The mean diastolic BP in the intervention group was 2.6 mmHg (95% CI: –5.5 to 0.15) lower compared to the usual care group.

Study	mHealth	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
(Pandey, 2015)	1. TM reminders for the 1 st month and no TM for the 2 nd month (n=15) 2. no TM in the 1 st month and TM reminders in the 2 nd month (n=15)	Stable cardiac patients (n=30)	N/A	Adherence was determined from patient medication logs by calculating the number of total prescribed doses and the number of doses actually taken as recorded in log books	Adherence to medication with TM reminder improved in 100% of cardiac patients, with a 64% RR reduction for nonadherence (P<0.01).	N/A
(Akhu-Zaheya and Wa'ed, 2016)	1. SMS regarding adherence to diet, medication, and smoking 2. placebo (general messages) (3m)	CVD patients (n=160)	Control group received routine care	MMAS, Mediterranean Diet Adherence Screener, and Readiness to Quit Ladder at the beginning and 3 m later	Significant differences between study groups found in terms of adherence to medication	Significant differences between groups in adherence to diet; no difference in intention to quit smoking
(Bobrow et al., 2016)	1. Information-only SMS (n=457) + reminders for medication collection, appointments 2. Interactive SMS (n=458): (weekly) 12-months	Adults (age ≥21 years) diagnosed with hypertension; prescribed BP lowering medication; with a systolic BP (SBP) <220 mm Hg and a diastolic BP (DBP) <120 mm Hg at enrolment (n=1372)	usual care (n=457) received no SMS	1. Change in systolic BP Adherence (PDC) in the clinical record, 2. EQ-5D scores, attendance at clinic appointments, retention in clinical care, treatment and clinic satisfaction, hypertension knowledge, self-reported adherence, hospital admissions and differences in medication changes	The number of participants who had at least 80% of PDC was 248 (62.8%) for the information-only group, 225 (59.7%) for the interactive group and 190 (49.4%) for usual care, (informative messages vs. usual care P<0.001, interactive messages vs. usual care P=0.002)	The mean (95% CI, P value) adjusted difference in BP change for the information-only group compared to usual care was -2.2 mm Hg (-4.4 to -0.04, P=0.046) and for the interactive group compared to usual care -1.6 mm Hg (-3.7 to 0.6, P=0.16).

Study	mHealth	Target Population	Comparison group	Described measures	Adherence outcome	Other outcomes
(Fang and Li, 2016)	1.SMS education and medication reminder, 2.SMS reminder + Micro Letter for education, and calls for 6m	Outpatients with CAD (n=280)	Control group received a telephone call once a month to remind them of their medication schedule and upcoming appointments	Adherence to statin prescriptions was compared among the groups by using the MMAS	The SMS and SMS + Micro Letter groups had better cumulative adherence after 6 months than phone group. The SMS + Micro Letter group had better cumulative adherence than the SMS group	Female sex, older age and marriage show positive associations with adherence.

Appendix 3: Patients' Socio-demographic Questionnaire

Subject ID:

1. Discharge Date:
2. Diagnosis:
3. Gender: Male = 1 Female = 2
4. Age:years
5. Marital status
 - 1 Married
 - 2 Single
 - 3 Divorced
 - 4 Other
6. Education level
 - 1 None
 - 2 Primary
 - 3 Secondary
 - 4 University
7. Are you currently employed?
 - 1 Yes
 - 0 No
8. Financial Resource
 - 1 Government Servant
 - 2 Self Sponsored
 - 3 Welfare Assistance
 - 4 Pensioner
 - 5 Other
9. Insurance
 - 1 Yes
 - 0 No
10. Average Income (Monthly):
11. Living Arrangement
 - 1 With family members
 - 2 With relatives
 - 3 With friends
 - 4 Alone
 - 5 Others
12. Length of stay in hospital (days):
13. Any other diseases:
14. Number of daily medications:
15. Medications:

Appendix 4: Patients' Perception Survey Questionnaire

Q No.	Question	Responses	Instructions
Q1	Do you routinely use cell phones?	1. Yes 2. No	If 'Yes' go to Q3 If 'No' go to Q2
Q2	Why do you not use a cell phone? (tick all that applies)	1. Lack of money 2. No network 3. Have no use for it 4. Inability to use 5. Other	Skip to Q10
Q3	Do you have a cell phone?	1. Yes 2. No	If 'No' skip to Q10
Q4	Is this phone mostly kept in your possession?	1. Yes 2. No, shared by ..	
Q5	Since when have you used cell phones?	____yrs	Fill in years
Q6	Do you use cell phones to talk?	1. Yes 2. No	If 'Yes' go to Q6a If no, skip to Q7
Q6a.	How often do you a. call others b. receive calls	____/day or wk ____/day or wk	Mark whether day or week.
Q7	Do you use the SMS function on your cell phones?	1. Yes 2. No	If 'Yes' go to Q7a If no, skip to Q8
Q7a	How often do you a. send SMS b. receive SMS	____/day or wk ____/day or wk	Mark whether day or week.
Q8	Do you use the alarm function?	1. Yes 2. No	If 'Yes' go to Q8a If no, skip to Q9
Q8a	What do you use the alarm function for? (tick all that applies)	1. To wake up 2. To remind me of errands 3. As a reminder for medicines 4. Other	Multiple answers possible.
Q9	What other use do you have for the cell phones? (tick all that applies)	1. Listen to radio 2. Play games 3. Camera 4. Other 5. None 6.	Multiple answers possible.
Q10	For a cardiac patient, would it be helpful to have automatic reminders on the cell phone to help remind the patient to take medicines?	1. Yes 2. No	If 'Yes' go to Q11 If 'No' skip to Q17

Q No.	Question	Responses	Instructions
Q11	If we were to provide automatic reminders to patients to take medications, what format would you like these reminders to be in?	<ol style="list-style-type: none"> 1. Telephone call (Voice format) 2. SMS message 3. Smartphone application 4. No preference 	Choose only 1.
Q12	Do you have a Smartphone?	<ol style="list-style-type: none"> 1. Yes 2. No 	If 'Yes' go to Q13 If No, skip to Q14.
Q13	Do you use Smartphone applications?	<ol style="list-style-type: none"> 1. Yes 2. No 	
Q14	If we were to provide automatic reminders for medication, how often would you like these reminders to be sent to the patient?	<ol style="list-style-type: none"> 1. As often as the medications need to be taken 2. Daily 3. Once a week 4. Twice a week 	Choose only 1 answer
Q15	If we provide automatic reminders, what times would you like the reminders to be sent to you?	<ol style="list-style-type: none"> 1. Just before the drugs timings 2. Morning: 6am – 10 am 3. Mid day: 11 am – 2 pm 4. Evening: 3 pm – 6 pm 5. Late evening/night: 7 pm – 10 pm 6. Anytime 	Choose 1 answer
Q16	Why is this time convenient for you?		Skip to Q18
Q17	Why do you think that these reminders for medication are not useful?		Write reasons.
Q18	If we were going to develop an application using cell phones for cardiac patients – what other possibilities do you think would be useful? (tick all that applies)	<ol style="list-style-type: none"> 1. Communication with health provider 2. Information on medicines 3. Motivational Messages 4. Other (Please specify) 	
Q19	Do you think the cell phone used in this way will be an intrusion in a person's life?	<ol style="list-style-type: none"> 1. Yes 2. No 3. Don't know 	
Q20	Do you prefer to send a reply message to each reminder when you take your medication?	<ol style="list-style-type: none"> 1. Yes 2. No 3. Don't know 	
Q21.	Can you please write your preferred medication reminder message content?		

Appendix 5: SCVI/Ave for the Survey Questionnaire

Items	Expert 1	Expert 2	Number in agreement	Item CVI
1	-	√	1	0.5
2	√	√	2	1
3	√	-	1	0.5
4	√	√	2	1
5	√	√	2	1
6	-	-	2	1
7	√	√	2	1
8	√	√	2	1
9	√	√	2	1
10	√	√	2	1
11	√	√	2	1
12	√	√	2	1
13	√	√	2	1
14	√	√	2	1
15	√	√	2	1
16	√	√	2	1
17	√	√	2	1
18	√	√	2	1
19	√	√	2	1
20	√	√	2	1
21	√	√	2	1
Proportion Relevant	0.90	0.90		Mean I-CVI = 0.95 S-CVI/UA = 0.85 S-CVI/Ave = 0.9

Appendix 6: Morisky Adherence Scale and Coding Instructions

<p>©Morisky Medication Adherence Scale (MMAS-8-Item). This is a generic adherence scale and the name of the health concern can be substituted in each question item. You indicated that you are taking medication for your (identify health concern). Individuals have identified several issues regarding their medication-taking behaviour and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your [health concern] medication.</p>		
<p>(Please check your response below)</p>		
	No=1	Yes=0
1. Do you sometimes forget to take your [health concern] pills?		
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your [health concern] medicine?		
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring along your [health concern] medication?		
5. Did you take your [health concern] medicine yesterday?		
6. When you feel like your [health concern] is under control, do you sometimes stop taking your medicine?		
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your [health concern] treatment plan?		

8. How often do you have difficulty remembering to take all your medications?

(Please circle your response below)

Never/Rarely.....4

Once in a while.....3

Sometimes.....2

Usually.....1

All the time.....0

Coding Instruction:

You will need to reverse the code response in a positive direction for item number 5 and standardize the code for item 8 (0-4), resulting in a scale from low adherence to high adherence. Item 8 is divided by 4 when calculating a summated score. This procedure standardizes the 5-point Likert scale. The total scale has a range of 0 to 8.0. The eight-item compliance scale had an alpha reliability of 0.83 (n= 1367) among patients diagnosed with essential hypertension attending an outpatient clinic of a large teaching hospital. We have used a 75% completion criterion for establishing eligibility. The median value of all non-missing items would be substituted for the missing item for individuals meeting the eligibility criterion.” I.e. if 1 or 2 items are missing, the median values of the other 7 or 8 items would be substituted for the missing item.

Re-codes:

If Item5 = 0 Item5r = 1 (high adherence)
If Item8=4 Item8r = 1 (highest adherence)
If Item8=3 Item8r = 0.75 (high adherence)
If Item8=2 Item8r = 0.50 (moderate adherence)
If Item8=1 Item8r = 0.25 (low adherence)
If Item8=0 Item8r = 0 (lowest adherence)

Adherence Level	Percent
Low Adherence (< 6)	32.1
Medium Adherence (6 to <8)	52.0
High Adherence (= 8)	15.9

Appendix 7: MMAS- 8 License Contract and Copyright Agreement

Required citation and footnote for the 8-item MMAS are as follows:

MMAS-8

Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive Validity of a Medication Adherence Measure for Hypertension Control. *Journal of Clinical Hypertension* 2008; 10(5):348-354

Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New Medication Adherence Scale Versus Pharmacy Fill Rates in Seniors With Hypertension. *Am J Manag Care* 2009;15(1):59-66.

Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. *J Clin Epidemio* 2011; 64:258-263. PMID:21144706

This footnote is required on all tables or figures which present the ©MMAS-8.

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B. Translations: Permission will only be granted to translate the MMAS tools subject to the following requirements: all new translations must be made by contracting with the MAPI Institute and final translations must be approved by the Owner. The MAPI Institute employs the most rigorous standards in the translation process using two native linguistic experts to independently conduct forward and backwards translation; the Owner is actively involved in validating each item in the scale and grants use of the translated scale through a separate license agreement that is linked to the License Agreement Contract/Copyright Agreement. Languages that have already been translated and validated by the MAPI Institute can be requested through the Owner/Developer, Dr. Donald E. Morisky.

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If I am eligible for a waiver of license fee contractual agreement, I agree to provide Dr Morisky with a detailed report that includes the specific number of MMAS-8 tests given and the findings upon completion of this study, cite the required references as noted on this waiver of license fee agreement and will comply with the copyright specification outlined above regarding the use of the Morisky Medication Adherence Scale, 8-Items, MMAS-8 and will abide with its requirements. If I fail to file the report within 30 days following the end of the study or after the one year period, I agree to pay Dr. Morisky a fee of \$500.

Please print, sign, and scan and email *this agreement to dmorisky@ucla.edu*

Please sign and return this contractual agreement in a PDF format, to Professor Morisky and he will provide you with the listing of the MMAS-8 items, scoring and

re-coding criteria and signature authorizing full use of this copyrighted scale. I agree to use only the English version of the MMAS-8 unless I purchase a validated translation of the MMAS-8 through Professor Morisky. I understand that it is a violation of international copyright laws to either use your own translation and call it the "MMAS-8" or use an existing MMAS-8 scale that has been translated and used for another study. The validated translation is non-transferrable and is linked to a specific license agreement and cannot be reproduced, copied, distributed, placed on the internet, published, or used by another individual. If the licensee violates any copyright laws contained in this licensing agreement they will be solely responsible for a \$5000.00 penalty and any associated legal costs.

Name and Contact Information of Licensee: Dr Aisha Holloway
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For doctoral student Sahar Khonsari

Title of Study: Development of a Mobile Health Intervention for Outpatients
Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication
Adherence

Total number of administrations:

Signature of developer/owner of the MMAS-8:

Donald E. Morisky, ScD, Developer/Owner of the MMAS-8/

Date Signed: 6/10/15







Signature of Licensee: Dr Aisha Holloway /

Date Signed: 6/10/15

The confirmation of payment for the validated Persian translation of the English MMAS-8 is presented below:

 DONALD MORISKY <dmorisky@ucla.edu>    
Sun 11/10/2015, 07:41

 Persian.doc 38 KB   2. MODEL Template for ... 45 KB 

2 attachments (83 KB) Download all Save all to OneDrive - University of Edinburgh

Good morning Aisha and here is your bank receipt and MMAS-8 docs.

Expand Transaction 0 with description : WIRE TRANS SVC CHARGE - SEQUENCE: 151007008152 SRF# SWF008989280
10/07/15 TRN#151007008152 RFB# PET585925280 WIRE TRANS SVC CHARGE - SEQUENCE: 151007008152 SRF# SWF008989280 \$16.00
TRN#151007008152 RFB# PET585925280
Expand Transaction 1 with description : WT SWF008989280 BARCLAYS BANK PL /ORG=UNIVERSITY OF BRISTOL SRF#
SWF008989280 TRN#151007008152 RFB# PET585925280 WT SWF008989280 BARCLAYS BANK PL /ORG=UNIVERSITY OF
BRISTOL SRF# SWF008989280 TRN#151007008152 RFB# PET585925280 \$746.00

Please let me know if you have need for any additional documents. Please remember that you must change the current "health condition" with you specific Health Condition. Items 1.2.4.5. 6 and 7 require this change. Please send me the translated name of your "health condition" after you make the modification in the Persian for Iran translation. I have attached the English listing of the MMAS-8, scoring and re-coding criteria, psychometric properties and frequency distribution of the categorical scale. Please put a reminder in your calender to send me a brief summary of your findings upon completion of your study as required for your waiver of license fee.

Best of success on your doctoral studies.

Prof Morisky

Appendix 8: The SF-12v2® Health Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf .. 1..... 2 3
- b Climbing several flights of stairs 1..... 2 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Accomplished less than you would like 1 2 3 4 5
- b Were limited in the kind of work or other activities 1 2 3 4 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Accomplished less than you would like 1 2 3 4 5
- b Did work or other activities less carefully than usual 1 2 3 4 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Have you felt calm and peaceful?..... 1 2..... 3..... 4..... 5
- b Did you have a lot of energy? 1 2..... 3..... 4..... 5
- c Have you felt downhearted and low?..... 1 2..... 3..... 4..... 5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

Appendix 9: The SF12V2 Health Survey License Contract and Copyright Agreement



NON-COMMERCIAL LICENSE AGREEMENT Office of Grants and Scholarly Research (OGSR)

License Number: QM029383
Licensee Name: Sahar Khonsari c/o University of Edinburgh
Licensee Address: 2/2 Blandfield, Edinburgh EH7 4QJ GB
Approved Purpose: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence
Study Name: Student Thesis/Dissertation
Study Type: Non-commercial academic research and/or thesis – Unfunded Student
Data Collection Method: Interview Script and Paper
Therapeutic Area: Bones, Joints and Muscles
Indication:

Royalty Fee: None, because this License is granted in support of the non-commercial Approved Purpose

A. Effective Date: This Non-Commercial License Agreement (the "Agreement") from the Office of Scholarly Grants and Research (OGSR) is made by and between OptumInsight Life Sciences, Inc. (f/k/a QualityMetric Incorporated) ("Optum"), 24 Albion Road, Building 400, Lincoln, RI 02865 and Licensee. This Agreement is entered into as of the date of last signature below and is effective for the Study Term set forth on Appendix B.


B. Appendices: Capitalized terms used in this Agreement shall have the meanings assigned to them in Appendix A and Appendix B. The appendices attached hereto are incorporated into and made a part of this Agreement for all purposes.


C. Grant of License: Subject to the terms of this Agreement, Optum grants to Licensee a non-exclusive, non-transferable, non-sublicensable worldwide license to use, solely for the Approved Purpose and during the Study Term, the Licensed Surveys, Software, SMS Scoring Solution, and all intellectual property rights related thereto ("Survey Materials"), in the authorized Data Collection Method, Modes of Administration, and Approved Languages indicated on Appendix B; and to administer the Licensed Surveys only up to the total number of Administrations (and to make up to such number of exact reproductions of the Licensed Surveys necessary to support such Administrations) in any combination of the specific Licensed Surveys and Approved Languages, Data Collection Method, and Modes of Administration.

EXECUTED by the duly authorized representatives as set forth below.

OptumInsight Life Sciences, Inc.

Sahar Khonsari
(Licensee)

Signature: 
Name: Michelle White
Title: Director of Consulting Science
Date: 22 APR 2015

Signature: 
Name: Sahar Khonsari
Title: PhD Student in Nursing Studies
Date: 22/04/2015

Appendix 10: Nurses' Socio-demographic Questionnaire

Subject ID
Gender	1. Female 2. Male
Ageyears
Education	1. Bachelor's 2. Master or Higher
Marital Status	1. Married 2. Single
Hospital Ward	1. Cardiac Rehabilitation 2. Cardiac Intensive Care 3. Hospital Nursing Department 4. Other Cardiology Wards
Position	1. Staff Nurse 2. Head Nurse 3. Supervisor 4. Ward Administrator
Working Experienceyears
Have you ever participated in any mHealth Seminars?	1. Yes 2. No

Appendix 11: Focus Group Discussion Topic Guide

- Welcoming and Introduction (short biography of researcher and participants)
- Describing the research study (aim, objectives and method)
- Description the study intervention (mHealth-based intervention)
- Asking questions:
 1. Have you ever heard of Mobile Health (mHealth)? If YES can you give examples of this. If NO then refer them back to the definition from the provided printed copy of the definition of mHealth.
 2. Do you have any experience of using mHealth in your current or previous clinical practice?
 3. What do you feel are the potential effects of using the proposed mHealth intervention (automated reminder system) on medication adherence of cardiac patients after discharge?
 4. What are the possible challenges/ barriers of using mHealth interventions to promote cardiac medication adherence?
 5. How can we address these challenges?
 6. In your opinion, what is the best strategy to implement the proposed mHealth intervention for cardiac patients?

Appendix 12: Medication Adherence Self-efficacy Scale

Situations	Not at all sure	Somewhat sure	Very sure
1. When you are busy at home			
2. When you are at work			
3. When there is no one to remind you			
4. When you worry about taking them for the rest of your life			
5. When they cause some side effects			
6. When they cost a lot of money			
7. When you come home late from work			
8. When you do not have any symptoms			
9. When you are with family members			
10. When you are in a public place			
11. When you are afraid of becoming dependent on them			
12. When you are afraid they may affect your sexual performance			
13. When the time to take them is between your meals			
14. When you feel you do not need them			
15. When you are travelling			
16. When you take them more than once a day			
17. If they sometimes make you tired			
18. If they sometimes make you tired			
19. When you have other medications to take			
20. When you feel well			
21. If they make you want to urinate while away from home			
Please rate how sure you are that you can carry out the following tasks ALL OF THE TIME:			
22. Get refills for your medications before you run out			
23. Make taking your medications part of your routine			
24. Fill your prescriptions whatever they cost			
25. Always remember to take your blood pressure medications			
26. Take your blood pressure medications for the rest of your life			

Appendix 13: New York Heart Association's Functional and Therapeutic Classification (NYHA) (1994)

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Appendix 14: Post-test Patient's Perceptions about the Applied Intervention

Perceptions items	Responses
Opinion on SMS reminders for taking medications?	1. Useful 2. No difference 3. Not useful
In which aspect this service helped?	1. As reminder 2. Support 3. Interaction with healthcare providers 4. Maintaining independence/ self-efficacy in taking medications
Want the SMS reminder to be continued in future?	1. Strongly agreed 2. Agreed 3. Neither 4. Disagreed 5. Strongly disagreed
Suggest this SMS reminder system to other patients?	1. Strongly agreed 2. Agreed 3. Neither 4. Disagreed 5. Strongly disagreed
SMS reminders may cause intrusion in a person's life?	1. Strongly agreed 2. Agreed 3. Neither 4. Disagreed 5. Strongly disagreed
Would you pay for receiving SMS reminders?	1. Strongly agreed 2. Agreed 3. Neither 4. Disagreed 5. Strongly disagreed
Recommendations to improve this service in future:	

Appendix 15: Letter of permission to use the Medication Adherence Self-efficacy Scale (MASES)

Request for the Medication Adherence Self-efficacy Scale (MASES)



Ogedegbe, Olugbenga <Olugbenga.Ogedegbe@nyumc.org>

To: KHONSARI Sahar;

Inbox

Hello,

I do not have a Persian Iranian version of this scale but you do have my permission to use the English version.
Good luck with your research!

Gbenga Ogedegbe, MD, MPH
Professor of Population Health and Medicine
Director, Division of Health and Behavior
Director, Center for Healthful Behavior Change

Vice Dean,
NYU Global Institute of Public Health

NYU School of Medicine
Department of Population Health
Translational Research Building
[227 East 30th Street, 6-633](#)
[New York, NY 10016](#)
Tel: 212-263-4183
Fax: 212-263-4201

Administrative Assistant: Johnni Lindsay
Tel: 212-263-4280
Email: johnni.lindsay@nyumc.org



Amir Pakpour <pakpour_amir@yahoo.com>

To: KHONSARI Sahar;



Fri 18/09/2015 12:03

Dear Sahar

The response to each item is formatted on a four-point Likert scale with 1=not at all sure, 2=a little sure, 3=fairly sure and 4=extremely sure. All responses were added to obtain a summary score with higher scores indicating greater self-efficacy.

There is no need to get permission from the original developer. We had done it already. You can use the Persian version.

Regards
Amir

Amir H Pakpour, Ph.D.
Assistant Professor of health psychology,
Director of Social Determinants of Health Research Center (SDH),
Qazvin University of Medical Sciences,
Qazvin, Iran.
Phone: +98-28-33239259
Fax: +98-28-33239259
Emails: Pakpour_Amir@yahoo.com
apakpour@qums.ac.ir
Address: Shahid Bahonar Blvd, Qazvin, Iran.
Postal Code: 3419759811
Cellphone: +98-9193144371

Appendix 16: Agreement with the Text Message Service Provider about the Patients' Data (Mobile Phone Numbers) Protection

Ticket History **KHONSARI Sahar** (Client) Posted On: 15 February 2016 01:57 PM

Dear Sir/ Madam

Greetings

I am a PhD student at the University of Edinburgh. I am writing to you because I would like to use your Text Message Services in my research project.

According to the data protection principles and Research Ethics, It is necessary for the researcher to be certain about the protection of human personal data (in this case: mobile phone numbers) before conducting the study. I am sure that you will understand that all these are for caring about privacy of people participating in a research and preventing any unethical act.

With considering these issues, could you please confirm that you will destroy provided mobile phone numbers after sending text messages?

Thank you very much for your consideration.

Kind regards

Sahar

(Staff) Posted On: 15 February 2016 02:58 PM

Hi Sahar,

Thanks for writing to Plivo Support.

We understand your requirements for privacy and as are happy to state that you have the option not to log the numbers to which the message was sent out.

The various parameters which can be used with the message API may be found here: <https://www.plivo.com/docs/api/message/>

The parameter 'log' may be of interest to you, when the 'log' parameter is set to false we will send out the message to the number in question but we will mask the number in the logs. It would not be possible to delete the number as a whole as it would get in the way of billing, invoicing, etc.

However, masking should help in maintaining the privacy of the recipients of the messages and the original numbers will not be retrievable.

Do let us know if this works for the purposes you have in mind or if you have any further queries.

Thanks & Regards,

KHONSARI Sahar (Client) Posted On: 16 February 2016 09:27 PM

Dear

Thank you very much for your reply.

Can you please clarify below queries:

1. What will happen to the phone numbers I provide you with to send text messages after I have finished using your services?
2. Can you please confirm that the phone numbers will not be sold or passed on to a third party without my explicit consent?

Hi Sahar,

Thanks for writing back.

With regards to the numbers you use with us, your account is accessible only to those who have access to your username and password. Should you use the 'log' parameter as previously suggested even these would not be visible from your account logs. These numbers of course, would not be made available to anyone else and even our own logs accessible to a very select few within the company would not show the number if it has been masked and these logs are also overwritten periodically.

Further, there is absolutely no question of us selling these numbers or any other information you provide to a third party in any case. Should such a proposal be made to us, it certainly would not be done without your express consent.

Please let us know if you have any further queries.

Thanks & Regards,

Appendix 17: University of Edinburgh Research Ethical Approval



Ref: NURS006

Sahar Khonsari
Doctoral Research in Nursing Studies
School of Health in Social Science
Medical School
Teviot Place
Edinburgh
EH8 9AG

SCHOOL OF HEALTH IN SOCIAL SCIENCE

The University of Edinburgh
Doorway 6
Medical Quad
Teviot Place
Edinburgh
EH8 9AG

6 May 2015

E-mail: k.melia@ed.ac.uk
Telephone: 0131 650 3893
Fax: 0131 650 3891

Dear Sahar

APPLICATION FOR LEVEL 2/3 APPROVAL

PROJECT TITLE: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence

Thank you for submitting the above research project for review by the Section of Nursing Studies Ethics Research Panel.

I can confirm that the submission has been independently reviewed and was approved on 29 April 2015

Should there be any change to the research protocol, it is important that you alert us to this as this may necessitate further review.

Yours sincerely

p.p. Kath Melia
Professor of Nursing Studies

Appendix 18: Tehran University of Medical Science Research Ethical Approval

Vice Chancellor for Research,
Tehran University of Medical Sciences,
Ghods St., Keshavarz Blvd,
Tehran, 1417653761,
I. R. Iran
Phone: 0098 21 88987381-2
Fax: 0098 21 88987382
Email: resdeputy@tums.ac.ir
Web: www.tums.ac.ir



In the name of God, the Beneficent, the Merciful

Ethical Approval

Title of Project: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence.
Ethics Approval Code: 92-04-28-28802-145738

Principal investigator: Alireza Nikbakht Nasrabadi

Approval Date: 2015/4/21

The Ethics Committee of Tehran University of Medical Sciences has approved the project in accordance with the tenets of the Helsinki Declaration and the national ethical guideline for medical research. Approval is granted on the conditions outlined below.

- Approval is given for three years. Projects, which have not commenced within two years of original approval, must be re-submitted to the Ethics Committee.
- Prior approval from the Ethics Committee is required before implementing any changes in the consent documents or any changes in the protocol unless those changes are required urgently for the subjects.
- You must complete and return the final report form when your research is completed.

The project is attached to this certificate.

M. Yunesian

Masud Yunesian, MD PhD
General Secretary, Ethics Committee and
Vice Chancellor for Research
Tehran University of Medical Sciences



Appendix 19: Participants' Information Sheets

Document Title: Patients' Information Sheet

Version: 1.1

Date:

Study Title: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence

You are invited to take part in a research study. Before you decide whether or not to take part, it is important you understand why the research is being done and what it will involve. Please read the following information carefully. If there is anything that is not clear please do not hesitate to contact me.

Introduction

The immediate discharge period is a time of high risk for non-adherence to prescribed medications. Nearly 1 in 4 patients is partially or completely nonadherent in filling prescriptions after discharge. Cardiovascular patients may face significant health problem related to the premature discontinuation of therapies after discharge. Evidence-based interventions that assist adherence to prescribed medications have the potential to delay disease progression and the development of complications, contributing to reduced health care costs for health systems and the people who use them. Therefore the researcher aims to develop mobile phone reminders and evaluate the effect of the intervention on medication adherence among outpatients Cardiac Rehabilitation.

What is the purpose of this study?

This study wishes to achieve a solution to medication non-adherence problem involved in supporting patients' adherence by focusing on the most common factors (forgetfulness and carelessness) which affect each individual to prevent complications, and improve patient health outcomes.

What are the procedures to be followed?

The mobile health reminder system will be introduced to patients in the first session of phase III cardiac rehabilitation, and then patients will be recruited into the study with their agreement. The participants' medications will be recorded in accordance with their physicians' advice. Each day following recruitment, medication reminders will be sent to patients' mobile phones automatically at predefined times in an 8-week programme.

Who should not enter the study?

- Those who are unwilling to participate in this study,
- Those who do not have cell phone to receive related text messages,
- Patients who are illiterate for reading text messages,
- Unavailability for the 2 months period of the study (including being unavailable by phone and/or travelling out of the country),
- Patients with a level of cognitive impairment
- Patients who are physically unwell or diagnoses with a terminal illness.

What will be benefits of the study?

(a) to you as the subject?

This study will employ automated reminders for medications follow-up care as a popular way which assist patient's medication adherence with rapid, effective guidance and pharmaceutical care after discharge. Hence the use of this free of charge medication reminders may improve pharmaceutical care, nurse-patient interaction, and the effect and safety of medication. It finally may lead to delay disease progression and the development of complications, and also may contribute to reduced healthcare costs for health systems and the people who use them.

(b) to the investigator?

This study will help investigator to complete the research project required for achieving postgraduate degree and to explore the effectiveness of a research-tested strategy as a complementary service to cardiac rehabilitation focused on medication adherence. The success of this study will indicate that mobile health intervention may improve the effect and safety of medication taking, clinical outcomes, and nurse-patient interaction after discharge.

What are the possible drawbacks?

There are no draw backs for the participants of this study.

Can I refuse to take part in the study?

Yes.

Who should I contact if I have additional questions during the course of the study?

Researcher's Name: Sahar Khonsari

Tel: Telephone number was added

Local Supervisor's Name: Professor Alireza Nikbakht Nasrabadi

Tel: Telephone number was added

Document Title: Staff Information Sheet**Version: 1.1****Date:****Study Title: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence**

You are invited to take part in a research study. Before you decide whether or not to take part, it is important you understand why the research is being done and what it will involve. Please read the following information carefully. If there is anything that is not clear please do not hesitate to contact me.

Introduction

The immediate discharge period is a time of high risk for non-adherence to prescribed medications. Nearly 1 in 4 patients is partially or completely non-adherent in filling prescriptions after discharge. Cardiovascular patients may face significant health problems related to the premature discontinuation of therapies after discharge. Evidence-based interventions that assist adherence to prescribed medications have the potential to delay disease progression and the development of complications, contributing to reduced healthcare costs for healthcare systems and the people who use them. Therefore the researcher aims to develop and evaluate the effect of mobile phone reminders on medication adherence in outpatients Cardiac Rehabilitation. During the first phase of the study, focus group interviews will be carried out to identify cardiac nurses' views and experiences towards mobile phone interventions improve medication adherence.

What is the purpose of this study?

As part of my PhD, I am conducting a study; developing mobile phone reminders to improve medication adherence of cardiac rehabilitation patients. I wish to gain an insight into the experiences of the cardiac nurses from their perspectives and identify potential barriers or challenges related to using mobile phone medication reminders based on their clinical observations and thoughts that then guide the development of an appropriate, patient-centred intervention.

What it will involve for you?

If you decide to take part in this research study, I will conduct a digitally recorded group discussion. This will take place at an appropriate time and place that will be arranged with you prior to the session. You must have a work experience in cardiac rehabilitation and/ or cardiology wards to participate in the study. The interviews will last for approximately 1 hour.

Do I have to take part?

Taking part is completely voluntary; you are not obliged to take part.

What will happen if I want to take part?

If you decide to take part in this research study, you will be asked to sign a consent form. The interview will be digitally recorded and then transcribed (written up). All written information gathered will be kept confidential; you will be allocated a code to

ensure you remain anonymous. The interview data and quotes from your interview will be used in my PhD thesis and/or in articles published in journals - once again all the data will be anonymously coded. Both the digital data and written data gathered will be stored securely on password protected computers in a locked room and may be kept until data analysis is deemed complete. You are free to withdraw from the study at any time, without giving any reason.

What are the possible drawbacks?

There are no draw backs for the participants of this study.

Can I refuse to take part in the study?

Yes.

Who should I contact if I have additional questions during the course of the study?

Researcher's Name: Sahar Khonsari

Tel: Telephone number was added

Local Supervisor's Name: Professor Alireza Nikbakht Nasrabadi

Tel: Telephone number was added

Appendix 20: Participants' Consent Forms

Document Title: Patients' Consent Form

Centre Number:

Study Number:

Participant Identification Number for this study:

CONSENT FORM

Title of Project: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence

Name of Researcher: Sahar Khonsari

Please initial box

- 1. I confirm that I have read the information sheet dated.....
(version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Edinburgh and Tehran University of Medical Sciences, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
- 4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.
- 5. I understand that my phone number will be shared with a text messaging service provider anonymously and my mobile phone number would not be sold or passed on to a third party in any case without my explicit consent.
- 6. I agree to take part in the above study.

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Document Title: Staffs' Consent Form

Centre Number:

Study Number:

Participant Identification Number for this study:

CONSENT FORM

Title of Project: Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence

Name of Researcher: Sahar Khonsari

1. I confirm that I have read the information sheet dated.....
(version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Edinburgh and Tehran University of Medical Sciences, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.
5. I give permission for the audio-recording of my interview and possible use of (anonymised) quotes using my exact words.
6. I agree to take part in the above study.

Name of Participant

Date

Signature

Name of Person taking consent


Date

Signature

Appendix 21: Permission Letter for Access to the Study Settings in Tehran (Persian and Translated Versions)

تاریخ : ۱۳۹۴/۰۲/۲۲
شماره : ۹۴/۲۰۹۵/۱۳۰/ص
پیوست : ندارد

بسمه تعالی




دانشگاه علوم پزشکی
تهران
معاونت پژوهشی

معاونت محترم پژوهشی دانشگاه علوم پزشکی ایران
ریاست محترم بیمارستان مرکز قلب تهران
ریاست محترم بیمارستان شریعتی

با سلام و احترام

به پیوست تصویر نامه شماره ۱۷۸/۱۳۰/و/۹۴ مورخ ۹۴/۲/۲۲ مجری محترم طرح پژوهشی باکد ۲۸۸۰۲ جناب آقای دکتر علیرضا نیکبخت نصرآبادی در خصوص معرفی سرکار خانم سحر خوانساری جهت انجام طرح و پایان نامه دکترای تحت عنوان (طراحی سیستم اتوماتیک یادآوری داروها و بررسی تاثیر آن روی مصرف داروهای بیماران بازتوانی قلبی) به حضورتان ارسال میگردد. خواهشمند است دستور فرمایید همکاری لازم بانامبرده بعمل آید. انشاءالله در آینده نتایج تحقیق به اطلاع آن واحد رسانیده خواهد شد.

دکتر مژگان کاربخش داوری
مدیر امور تحقیقات و فناوری دانشگاه

بلوار کشاورز ، نبش خیابان قدس ، سازمان مرکزی دانشگاه ، طبقه ششم- تلفن ۲-۸۸۹۸۷۳۸۱ فاکس ۸۸۹۸۹۶۶۴
www.tums.ac.ir/research
Email: resdeputy@tums.ac.ir

Translated -version:

In the name of God, the Beneficent, the Merciful

Date: May 12, 2015

Number: 94/S/130/295

Appendix: None

Vice Chancellor
for Research,
Tehran University
of Medical
Sciences Tehran
University of
Medical Sciences
Vice Chancellor
for Research

Dear Vice Chancellor for Research in Iran University of Medical Sciences

Dear Vice President of Tehran Heart Centre

Dear Vice President of Dr. Shariati Hospital

Title of Project: Development of a Mobile Health Intervention for Outpatients
Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication
Adherence. Ethics Approval Code: 92-04-28-28802-145738 Approval Date:
2015/4/21

Principal investigator: Alireza Nikbakht Nasrabadi

PhD student: Sahar Khonsari

are introduced to you. Please cooperate with them in conducting the above research
project.

Research findings will be reported to you at the completion of the study in future.

Dr. Mojgan Karbakhsh Davari

Director of Research and Technology

Tehran University of Medical Sciences

Signed

Appendix 22: The study Setting Ethical Approval (Persian and Translated Versions)



مرکز قلب تهران

تاریخ: ۹۴/۷/۸
شماره: ۲۴۵۳
پیوست: قرارداد



دانشگاه علوم پزشکی
و خدمات بهداشتی
درمانی تهران

سرکار خانم خوانساری

با سلام

به استحضار می‌رساند پروپوزال پیشنهادی سرکارعالی با شماره ثبت ۷۶۸ تحت عنوان " طراحی سیستم اتوماتیک یادآوری داروها و بررسی تاثیر آن روی مصرف داروهای بیماران بازتوانی قلبی " در تاریخ ۹۴/۷/۶ در صد و بیست و ششمین جلسه شورای پژوهشی مطرح و با انجام آن با اعمال نظر شورای پژوهشی موافقت شد.

دکتر سعید صادقیان

معاون پژوهشی مرکز

شماره: ۱۰۰۳۶

تلفن: ۶۹-۸۸۰۲۹۶۰۰
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Appendix: None

Dear Mrs. Sahar Khonsari

Greetings

That is to inform you that your research proposal numbered 768 entitled: “Development of a Mobile Health Intervention for Outpatients Cardiac Rehabilitation: A Feasibility Study to Evaluate Impact on Medication Adherence” has been reviewed and approved in the 126th Research Ethics Committee Meeting on September 28, 2015.

Dr Saeed Sadeghian

Vice Chancellor of Research

Tehran Heart Centre

Signed