Protocol Title

Behaviour Change Interventions to Improve Medication Adherence in Patients with Cardiac Disease

Version Number: 2

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SYNOPSIS

Protocol title: Behaviour Change Interventions to Improve Medication Adherence in Patients with Cardiac Disease.

Protocol version: version (1)

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Summary

Study title: Behaviour Change Interventions to Improve Medication Adherence in Patients with Cardiac Disease.

Protocol version: 1

Objectives

Primary objective:

- To detect medication non adherence.
- To explore individual, behavioural and environmental factors that hinder medication adherence.

Secondary objectives:

- To examine the effectiveness of a multifaceted intervention comprising motivational interviewing techniques plus text message reminders to enhance adherence to cardiac medications.

Study design: Sequential mixed methods with nested pilot Randomised Controlled Trial (RCT).

Planned sample size: 28 participants.

Selection criteria:

1. 18 years of age or older.
2. Diagnosed with cardiac disease by their physician and referred to the cardiac rehabilitation program at POWH.
3. Prescribed at least one cardio-protective medication at least 7 days prior to recruitment.
4. Must also be able to speak, read and understand English.
5. Own a personal mobile phone, and be able to receive and reply to phone calls and text messages.

Exclusion Criterion:

1. Clinically identified or formally diagnosed with cognitive impairment; blind or deaf.

Study procedure

Statistical considerations: The sample will be selected from a consecutive cohort of patients referred to cardiac rehabilitation for cardiac disease secondary prevention.

Sample size calculation:

- With alpha = 0.05 (2sided), power= 0.80 (beta= 0.20).
- With consecutive sampling and allowing for 50% loss to follow-up.
- A sample size of 28 participants for both groups will be recruited (Ma et al. 2014).

Recruitment and screening: Patients referred to Cardiac Rehabilitation at POWH will be screened by the Clinical Nurse Consultant (CNC) as they attend their first session. For Phases One and Two, eligible patients will:

- Have an established diagnosis of cardiac disease by their physician;
- Will have been prescribed at least one cardio-protective medication at least 7 days prior to recruitment;
- They must have primary responsibility for taking their medication themselves (i.e. whilst a carer may play a role in supporting or promoting medication taking, they should not be identified as being accountable for ensuring the patient's adherence to their medication schedule);
- Patients must not be clinically judged as affected by cognitive impairment and must be able to speak, read and understand English, own a personal mobile phone, and be able to receive and reply to phone calls and text messages.

All patients recruited will complete a paper-based survey (phase one) and a brief face to face interview (phase two).

For the Pilot Trial Phase:

- Participants identified as 'non-adherent' to at least one of their cardiac medications, based on the result of exploratory phases of the study (survey and interview), will be invited to participate in the final pilot randomised trial phase.

Patients recruited to the pilot trial phase will be randomly allocated to either an intervention or control arm.

Intervention: Participants in the intervention group will receive usual care plus behavioural counselling about medication adherence using motivational interviewing (MINT) techniques and text message reminders.

Control group: will receive the usual cardiac rehabilitation program.

Analysis plan: Phase one: Descriptive statistics; Phase two: thematic analysis; Pilot trial Phase: descriptive statistics and inferential data analysis.

Duration of the study: The total duration of the study will be 12 months (six months for recruitment and six months participation for each participant recruited).

TABLE OF CONTENTS

1. BACKGROUND

1.1. DISEASE BACKGROUND

In recent decades coronary heart disease (CHD) has become a global health concern (Zhu et al., 2015). The prevalence of cardiovascular disease (CVD) is rapidly rising worldwide because of changing lifestyles adding challenges for both patients and healthcare providers (Hauptman, 2008). CVD has emerged as a leading cause of death and disability worldwide, particularly in developing countries (Gaziano, 2005). The prevalence of the disease increases with age and affects one in six Australians, ranging from 35% of those aged 55-64 years to 62% of those aged 75 years and over (Australian Bureau of Statistics, 2012). The prevalence of CVD increases with the presence of one or more major risk factors, including: family history, hypercholesterolemia, hypertension, diabetes, smoking, obesity, and physical inactivity (Australian Bureau of Statistics, 2012). Although a large proportion of CVD is preventable, the incidence of the disease remains high. In Australia, as in other developed countries, the prevalence and incidence of CVD has continued to increase in recent years regardless of advances in medical technologies and development of prevention programs (Australian Bureau of Statistics, 2012). Cardiovascular disease imposes significant burden on individuals and the health care systems in this country. It is the single greatest cause of death in Australia, accounting for the deaths of 21,867 males and 23,755 females in 2011 (Australian Institute of Health Welfare, 2014). In Australia, CVD is also the main reason of rehospitalisation, accounting for 524,000 hospitalisations in 2011/12 (Australian Institute of Health Welfare, 2014). According to AIHW (2010), CVD was responsible for 16% of the total burden of all diseases, which translated to AU$5.94 billion and equated to 11% of total health expenditure of Australia in 2004–2005 (Australian Institute of Health and Welfare, 2010).

Adherence to medications is a serious challenge, particularly in patients with chronic conditions such as cardiac disease who often need to take multiple medications for long periods (World Health Organisation, 2003). Numerous types of cardiac medication are available and have been proven effective for symptom management and slowing the progression of CVD. Multiple long-established and newer medications, such as angiotensin converting enzyme [ACE] inhibitors, β-blocking agents, aldosterone inhibitors, aspirin, statins and warfarin are prescribed to inhibit the progress of the disease and control its symptoms (Albert, 2008, Wu et al., 2008). The risk of mortality and morbidity in patients with cardiac disease increases if adherence to prescribed medication is poor (Hope et al., 2004). Medication non-adherence in patients with cardiac

conditions varies between 33% to more than 50% (Li et al., 2012, Munger et al., 2007, Shah et al., 2013), contributing to increased numbers of cardiovascular-related Emergency Department (ED) visits, rehospitalisation, poor health and well-being, augmented healthcare costs and risk of death ((Ashton et al., 1995, Mukhtar et al., 2014, Munger et al., 2007).

1.2. RATIONALE FOR PERFORMING THE STUDY

This proposed project aims to fill in the gap in the literature by developing and testing the effectiveness of an intervention designed to enhance adherence to cardio-protective medication in cardiac patients. This study will focus on cardiac patients with low-adherence, and apply adherence interventions to improve adherence in these patients. Appropriately designed interventions that utilise multiple approaches such as motivational interviewing targeting behaviour change, and reinforcing behaviours with text message strategies are likely to significantly increase medication adherence in cardiac patients (Al-Ganmi et al. under review). This study aims to evaluate the effectiveness of a theory based intervention on medication adherence in a robust pilot trial using RCT design. If effective, this nurse-led intervention could be implemented in cardiac rehabilitation programs in Australia to help improve patient adherence and enhance the effects of medical therapy and result in improved patient and disease outcomes, such as reduction in disease symptoms, recurrent cardiac events, rehospitalisation and mortality.

Non-adherence is a multifactorial phenomenon, affected by socio-economic status, health systems, disease states, pharmacological therapies and patient beliefs (Sabaté, 2003). For the purpose of this study, non-adherence is defined as “taking less than 80% of prescribed doses that can also include taking too many doses” (Nieuwlaat et al., 2014). In order to reduce the risk of recurrent cardiac events, it is important to identify factors that influence adherence and tailor supportive interventions that can help achieve improvement in patients adherence to their medication regimens (Munger et al., 2007).

Hypothesis

The study hypothesis is that motivational interviewing (MINT) counselling and text message reminders delivered in an outpatient setting in addition to standard care will enhance maintenance of medication adherence in cardiac patients compared to standard care alone.

Underpinning evidence and assumptions of the hypothesis are that:

1) A high proportion of patients fail to adhere to their cardiovascular medication regimens.

2) Medication adherence self-efficacy, patient beliefs and lack of social support are factors associated with non- adherence to medication.
3) High quality evidence supports use of multifaceted interventions comprised of motivational interviewing (MINT) counselling combined with text messaging reminders to improve medication adherence.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVES (PHASE 1 AND 2) AND OUTCOMES

1. To determine self-reported adherence or non-adherence to prescribed cardiac medications in cardiac patient referred to a cardiac rehabilitation program. The outcome will be self-reported medication adherence/non-adherence.

2. To explore individual, behavioural and environmental factors that affect adherence to cardiac medications. The outcome will be identification of factors that influence adherence to medications.

2.2. SECONDARY OBJECTIVE (PILOT TRIAL PHASE) AND OUTCOMES

To conduct pilot-testing of the hypothesis that, compared to standard care alone, standard care plus a multifaceted intervention comprising motivational interviewing techniques and text message reminders will enhance cardiac medication adherence among cardiac patients referred to attend cardiac rehabilitation program. The primary outcome will be medication adherence/non-adherence rate at six months/ change in medication adherence between baseline and 6 months scores.

3. STUDY DESIGN

3.1. DESIGN

The design of this study is sequential mixed methods with a nested pilot Randomized Controlled Trial (RCT); three interrelated phases, as:

Phase one: A survey design will be used to identify cardiac patients' medication adherence/non-adherence patterns and the factors that are most strongly associated with their medication non-adherence. The purpose of the survey is to gather quantitative data about medication adherence, patient behaviours, beliefs and other factors associated with medication non-adherence as well as

patients' demographic data. Paper based questionnaires will be used. The questionnaires will be self-administered, simple and easy to complete, and suitable for participants with low literacy.

Phase two: Semi-structured interviews will be used to gather descriptive qualitative data to explore the phenomenon of cardiac patients' adherence to medications and how they respond to factors that affect medication adherence. Semi-structured interviews will be used to explore views of patients about their cardiac medications, and factors that influence their medication adherence. Semi-structured interviews were chosen because this is a flexible method of collecting self-report data and allows the researcher to prepare questions ahead of time (Cohen and Crabtree, 2006). Semi-structured interviews will allow participants to cover all the study questions and by encouraging participants to talk freely about issues related to their medication adherence and tell stories in their own words, this method provides as much detail as the researchers wish (Polit and Beck, 2004). Semi-structured in-depth interviews will involve open-ended, direct, and verbal questions to elicit detailed narratives and stories building on an interview guide (Whiting, 2008). This will provide in-depth understanding, supplement and explain quantitative results from Phase one.

Information generated from phases one and two will be used to identify participants eligible to take part in the pilot trial phase, and synthesized to inform motivational interviewing processes aiming at addressing individual patients' medication adherence-related needs and support patients' adherence to their cardiac medications;

Pilot trial phase: Patients identified as non-adherent based on the result of exploratory phases (phase one and two) will be invited to participate in the pilot randomised controlled trial phase. This pilot RCT will test the effectiveness of a multifaceted intervention, comprising motivational interviewing (MINT) plus text message reminders, to influence the adherence of patients to their cardiac medications. The RCT will compare the effect of a multifaceted intervention with current standard care to enhance medication adherence outcomes. The control group will receive the standard usual care cardiac rehabilitation program and they will complete the baseline and follow-up questionnaires.

3.2. STUDY GROUPS

Participants will be cardiac patients referred to a cardiac rehabilitation program following their hospital admission for acute cardiac events; those participating in the pilot trial phase will be randomly allocated to receive either the intervention plus usual care or usual care only.

Intervention group: Participants in the intervention group will receive usual care plus behavioural counselling about medication adherence using MINT techniques and text message reminders. Each patient will receive approximately 30-40 minutes of a single MINT counselling session following recruitment (Appendix D) (Ma et al., 2014). The core of motivational interviewing is for the counsellor to be simultaneously sympathetic and supportive, as well as directive in moving patients toward change by strengthening their own reasons for change (Levensky et al., 2007). As part of the MINT counselling, the researcher has the opportunity to provide information that the patient may need or to explore some of the barriers that keep this patient from adherence to medications (Dart, 2010). Text message reminders (TM) (Appendix E) will be sent to these participants: one text message daily for two weeks, then on alternate days for two weeks and then on a weekly basis for the next 6 months (Wald et al., 2014). The content of the text message reminders will vary according to the patients' non-adherence factors. An example of the text message reminder is:

'Hello Mr/Mrs……. Have you refilled your heart medication today? Please text back "Y" if your answer is "Yes, I have refilled my medication before receiving this text", "R" if your answer is "the message has reminded me, I will refill my medication" and "N" if your answer is "No". Thank you. Ali and the research Team'.

The researchers will use a structured MINT counselling script (Appendix D) designed for patients with low adherence to medications, with each session tailored to the medication adherence characteristics of the individual patient (Dart, 2010). All MINT sessions will be audio taped and reviewed by a clinician qualified in MINT to ensure fidelity to the technique (Ma et al., 2014).

Control group: Patients randomised to the control group will receive standard care alone for the study period. They will be contacted at baseline and 6 months to complete the same measurements and interviews as the intervention group.

3.3. NUMBER OF PARTICIPANTS

The researcher will sample of a cohort participants referred to cardiac rehabilitation for phases one and two until adequate numbers have been recruited for pilot trial phase. To calculate the sample size for the study, the researcher used values for the means (*M*) and standard deviation (SD) based on data from Ma et al. (2014) using the following formula:

Cohen's $d = M1 - M2 / \sigma$ pooled, where σ pooled $=\sqrt{[(\sigma 12 + \sigma 22) / 2]}$

M1= means for group 1 = 29.72±3.46
M2= means for group 2 = 25.30 ±3.11

The resultant value for 2 sided test for alpha = 0.05, with power = 0.80, is a sample size of 9 for each group. Based on the results of the sample size calculation formula, 9 participants with complete data in each group will be required to detect a difference in the means of 4.42 points for the primary outcome at 6 months, assuming a common standard deviation of 3.285, with a power of β = 80% and a two-sided α value of 0.05. Assuming up to 50% attrition, a total of 28 participants will be recruited for pilot trial phase.

3.4. NUMBER OF CENTRES

The cardiac rehabilitation center at Prince of Wales Hospital (POWH).

3.5. DURATION

It is estimated that more than 350 patients attend the cardiac rehabilitation unit at POWH every year with an estimated 29 patients per month. Based on the recruitment criteria, the anticipation that not all patients will agree to participate and that the rate of recruitment must be manageable for the researcher, recruitment duration is estimated to take up to six months to recruit 28 participants. Hence, the duration of the study will be approximately six months for recruitment and a six months intervention and follow-up period.

4. PARTICIPANT SECTION

4.1. INCLUSION CRITERIA

1) 18 years of age or older;
2) Established diagnosis of cardiac disease by their physician and referred to the cardiac rehabilitation program at POWH;
3) Prescribed at least one cardio-protective medication at least 7 days prior to recruitment;
4) They must have primary responsibility for taking their medications themselves (i.e. whilst a carer may play a role in supporting or prompting medication taking, they should not be identified as being accountable for ensuring the patient's adherence to their medication schedule);

5) Participants must be able to speak, read and understand English, own a personal mobile phone, and be able to receive and reply to phone calls and text messages;

6) They must be willing to give written or oral informed consent to participate to in the study.

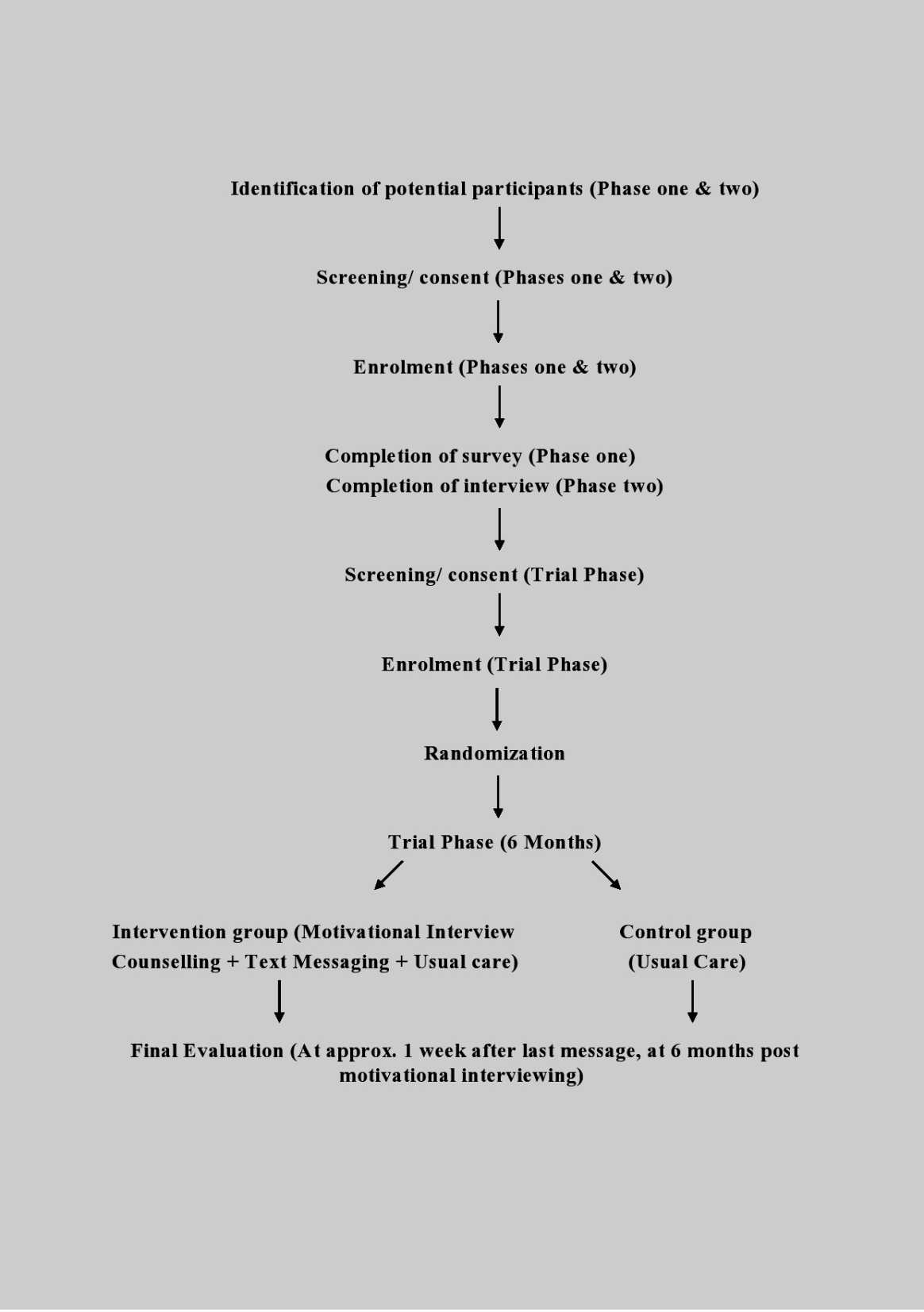
7) To be eligible for the trial phase, patients must be identified with at least one medication non-adherence factor, indicated by results of the medication adherence questionnaire and responses to the interview questions.

4.2. EXCLUSION CRITERIA

Patients who are deaf, blind or unable to accept phone calls will be excluded. Those clinically judged with cognitive impairment that limits their ability to understand and answer study questions will be excluded.

5. STUDY OUTLINE

5.1. STUDY FLOW CHART



5.2. INVESTIGATION PLAN

Interventions	Enrolment Visit	Visit 1	Visit 2	Telephone call or home visit
Screen for Inclusion / Exclusion criteria	✓			
Informed Consent	✓			
Survey	✓			✓
Semi-structured interview		✓		
Motivational interviewing			✓	

Patients referred to the cardiac rehabilitation at POWH are routinely booked for a 6 week cardiac rehabilitation (CR) program, delivered during one session per week. The enrolment visit, visit 1 and visit 2 of the study will occur during times when the participant is booked to attend CR.

The final data collection point will occur at 6 months post recruitment. Participants will be asked to agree a convenient time when they can complete the questionnaire by telephone or by home visits from the researcher.

5.3. STUDY PROCEDURE

This study will be conducted in accordance with ethical standards established by the Australian Research Council and the National Health and Medical Research Council (National Health and Medical Research Council, 2015). Recruitment will occur under the supervision of the Clinical Nurse Consultant for cardiac rehabilitation with the agreement of the director of nursing and the cardiology consultant.

5.3.1. PHASE ONE (QUANTITATIVE EXPLORATORY SURVEY)

Sample and sampling approach: The method of consecutive sampling will be used. This technique involves selecting all eligible participants who agree to participate, provided they meet inclusion criteria, until a desired number of participants has been recruited (Schuster and Powers, 2005). The survey sample will be selected as a consecutive cohort of patients referred to cardiac

rehabilitation for cardiac disease secondary prevention. Cardiac patients eligible to participate will be identified by the Clinical Nurse Consultant in Cardiac Rehabilitation as they attend for their first session of cardiac rehabilitation. Those interested will be referred to the researcher, who will explain the survey (phase one) and the semi-structured interview (phase two) and will provide them with an information statement sheet and consent form. These two study phases will identify patients who are non-adherent with at least one cardiac medication who will be eligible to participate in the pilot trial phase (phase three). The survey and semi structured interviews will also identify factors that impact on the patients' adherence to cardiac medications.

Questionnaire Instrument: The instrument consists of a number of questionnaires to gather data about medication adherence, patient behaviours, beliefs and other factors associated with medication non-adherence (**Appendix A**). The questionnaires will be paper based, self-administered, simple and easy to complete, and suitable for participants with low literacy skills. Data collected will include demographic data: age, gender, marital status, social background (next of kin/ carer), home domicile situation, level of education, literacy, and ethnicity / country of birth; and clinical data: disease diagnosis and co-morbidities (**Appendix B**). Medication practices will be explored using the following instruments:

- Medication Adherence Questionnaire (Morisky et al., 1986).
- Adherence to Refills and Medications Scale (Kripalani et al., 2009).
- Belief about Medicine Questionnaire (Horne et al., 1999).
- Medication Adherence Self-Efficacy Scale-Revised (Fernandez et al., 2008).
- Medication Specific Social Support (Lehavot et al., 2011).

Non-adherence to medications will be assessed by the **Medication Adherence Questionnaire (MAQ)** designed to measure medication adherence behaviour and barriers such as forgetfulness, carelessness, adverse effects and efficacy. MAQ includes simple four-item dichotomous questions, scoring one point for each yes response; total scores are categorised as: 0 point indicating high; 1-2 points medium, and 3-4 points low medication adherence behaviour.

The **Adherence to Refills and Medications Scale (ARMS)** will be used to determine the patient medication adherence behaviour in terms of self-regulation. The ARMS comprises a 12-item scale with the first 8-item medication taking subscale assessing correct self-administration ability for the prescribed regimen. The next 4-item prescription refill subscale assesses the patient's ability to refill medications on schedule. Each item is scored on a four point scale ranging from l=

none of the time to 4= all the time. The higher numbers on the scale demonstrate patient's better ability to refill medications on schedule.

The **Belief about Medicine Questionnaire (BaMQ)** elicits information on patients' beliefs about their medicines where they may relate to adherence. It identifies whether the patient holds beliefs that their medicines are necessary or if they have concerns about their medicines. The study will use the short version of the BaMQ (the 8-item) developed by Horne et al., 1999. This version is composed of four subscales containing two items each, and assessing: General Harm; General Overuse; Specific Necessity; and Specific Concerns. Respondents indicate their degree of agreement with each statement on a five point Likert scale, ranging from l=strongly disagree to 5=strongly agree. The lower numbers on the scale demonstrate the patient's strong beliefs about taking medications. Scores are summed to give a total score, with higher scores indicating more positive beliefs. The focus of the BaMQ, is identification of barriers to medication adherence, contributing to comprehensive evaluation of the drivers behind medication adherence.

The **Medication Adherence Self-Efficacy Scale-Revised (MASES-R)** consists of 13 items that evaluate an individual's judgment of their ability to adhere to prescribed medications under a variety of challenging situations. Twelve of the items ask about patient confidence in taking medications in specific situations (e.g. busy at home, no symptoms, traveling), and one item addresses confidence in ability to make medication adherence as part of daily routine. Each item is scored on a four point scale, ranging from: 0= Not at all sure, 1= A little sure, 2= Fairly sure, and 3= Extremely sure. A single scale score is presented, the mean of all item scores. Higher scores on the scale indicate higher confidence.

The **Medication Specific Social Support (MSSS)** is an 8-item survey of medication-specific social support to identify how often others may have helped patients with their therapy, with scored for each item ranging from 0 (never) to 4 (very often). A single mean score is presented of medication-specific index of support.

These instruments have demonstrated rigor; see Table 1.

Table 5: The reliability and validity of the selected study instruments

Concept	Name of Questionnaire	Number of Items	Validity Test	Reliability Test Score
Medication Adherence behaviours & barriers	Medication Adherence Questionnaire (MAQ)	•Four-item questionnaire measure medication adherence behaviour specifically, barriers such as; forgetfulness and carelessness, & adverse effects & efficacy	Validated in patients with hypertension, dyslipidaemia, heart failure, and CAD	Cronbach's α = 0.61
Medication Adherence Behaviour (Self-Regulation)	Adherence to Refills and Medications Scale (ARMS)	•12-item scale. •The first 8-item medication taking subscale assess correct self-administer prescribed regimen ability. • The next 4-item prescription refill subscale assesses a patient's ability to refill medications on schedule	Validated in patients with CAD & other chronic diseases	Cronbach's α = 0.81
Medication taking beliefs	Belief about Medicine Questionnaire (BaMQ)	•8-item short version. • The 4-BaMQ subscales are containing two items each includes: General Harm; General Overuse; Specific Necessity; & Specific Concerns on a five point Likert scale.	BaMQ significantly correlated with other adherence scales: MAQ, Morisky Medication Adherence Scale (MMAQ), & medication adherence rating scale (MARS-5)	Cronbach's α = 0.70
Medication Adherence Self-Efficacy	Medication Adherence Self-Efficacy Scale-Revised (MASER-R)	• 13 items scale. • assess individual's judgment of their ability to adhere to medications under a variety of challenging situations	MASES-R assessed against electronic medication adherence & correlated positively & significantly.	Cronbach's α =0.91
Social Support	Medication Specific Social Support (MSSS)	•8-item survey • identify how often others may have helped patients with their therapy. • 4 point Likert scale.	Not stated	Cronbach's α = 0.92

Survey procedure: Participants will be asked to complete the paper-based survey instrument when they attend cardiac rehabilitation; they will be encouraged to complete it whilst they are at the hospital and to deposit it into a provided box in the cardiac rehabilitation venue. Participants can also complete the survey questionnaires at home and post it back via mail using the enclosed prepaid envelope if they prefer. The survey instrument will be printed in large font size and formatting for easy reading by older participants.

5.3.2. PHASE TWO (QUALITATIVE EXPLORATORY SEMI-STRUCTURED INTERVIEW)

Sample and sampling approach: Participants for this phase will have already participated in phase one of the study (See phase one). All participants who complete the survey (**Appendix A**) will be eligible to participate in the interview regardless of their survey results (i.e. whether or not the survey indicates they are adherent or non-adherent to their medications).

Interview schedule: A schedule of open-ended questions has been developed based on the literature to address the second primary objective of the study; this may be modified by the researcher based on results from phase one (**Appendix C**).

Interview procedure: Consent for this phase of the study will be obtained as the same time when participants give consent to Phase one and will be checked with participants prior to starting the interview. The semi-structured interviews will be conducted during a face to face meeting between the researcher and participants guided by a set of questions (Polit and Beck, 2004). The times and locations of the interviews will be arranged with participants to coincide with their routine visits to cardiac rehabilitation. Interview date and time will be arranged with participants at the visit when the survey is distributed, with a telephone reminder text two days before the scheduled interview.

Interviews will be digitally audio-recorded and transcribed by the researcher for analysis. The researcher will facilitate the discussion and create a comfortable environment. The setting chosen for the interviews will be neutral, comfortable, not intimidating, accessible, and amenable to audiotape recording (Polit and Beck, 2004). One of the meeting rooms at POWH will be used. Participants will be encouraged to talk about their beliefs and attitudes on taking medications as well as perceived barriers and facilitators. The researcher will take notes of the participants' body language and other non-verbal cues. Semi-structured interviews are anticipated to take up to 30-45 minutes. Immediately after each interview, the researcher will debrief participants while the recorder is still running and will label all tapes and notes with the date, time, and participant code.

5.3.3. PILOT TRIAL PHASE (PHASE THREE)

Sample and sampling approach: Patients identified as 'non-adherent', based on the results of exploratory phases (Phase one and Phase two), will be invited to participate in the pilot randomised trial phase.

5.4. RECRUITMENT AND SCREENING

Patients identified as 'non-adherent' to at least one of their cardiac medications based on the result of exploratory phases (Phase One and Phase Two) will be invited to participate in this pilot

randomised trial phase. Participants will be assessed as adherent or non-adherent based on the response to the Medication Adherence Questionnaire (MAQ). Patient with a total score of 1-2 will be considered as "adherent", and those with a total score of 3-4 as "non-adherent". At conclusion of the interview (Phase Two), eligible participants who are identified as "non-adherent" will be informed about Phase 3, the pilot RCT trial phase.

5.5. INFORMED CONSENT PROCESS

Prior to conducting the research, the researcher will obtain informed and voluntary consent from participants for phases one and two, and separately for the pilot trial phase. All prospective participants will be informed of the study purpose via participant information sheets. The participant information sheets will contain information about the purpose and objectives of the research as well as an explanation of what will be required of a participant during each phase, how research data will be gathered and analysed and what will happen to the information once the research is complete.

The researcher will provide an enrolment folder to the patient including written information about the study, a copy of their consent in addition to face to face explanation of the study. Written consent will then be sought to participate in Phases one and two.

At conclusion of the interview (Phase Two) eligible participants will be informed about phase three, the pilot RCT trial phase. A participant information sheet specific to this phase will be provided to the eligible participants and verbal and written consent will be obtained prior to randomisation for the pilot trial phase. Contact details for the researcher will be provided and prospective participants invited to ask questions about the research during discussions/ the consent process and/or via phone, email or text message if they wish to do so.

5.6. RANDOMISATION PROCEDURE: PILOT TRIAL PHASE ONLY

In pilot trial phase participants will be randomly allocated to receive either multifaceted intervention comprising current standard care plus motivational interviewing (MINT) follow by text messages or current standard care alone. Participants will be randomised after they have consented to participate in the trial phase, so that the decision to participate has no bearing on which arm of the trial they are allocated to. A random sequence will be generated by computerised random number generator and using permutated blocks in order to assure equal numbers in each arm, balanced at set intervals at 1:1 ratio.

6. SAFETY

In spite of all reasonable precautions, there is small potential anticipated risk, that participants may feel uncomfortable in sharing personal feelings about not following their medication regimen.

If phases one or two reveal medication practices that comprise a real and present risk to the patients' health and safety, this will be discussed with the study pharmacist and cardiac consultant, as indicated. The researcher will obtain patients' agreement that they seek further information and help from their General Practitioner (GP) if the study reveals they have problems related to how they take their heart medications and they remain unable or unwilling to take them as prescribed despite the intervention.

7. BLINDING AND UNBLINDING

Neither participants nor researcher can be blinded to the group allocation of participants (intervention or usual care only groups).

8. STATISTICAL CONSIDERATIONS

Sample Size or Power Calculation

Sample size for the RCT was calculated based on data from Ma et al. (2014). The researcher predefined and utilised the value for the means (*M*) and standard deviation (SD) based on Ma et al. using the following formula:

$$\text{Cohen's } d = M_1 - M_2 / \sigma_{\text{pooled}}, \text{ where } \sigma_{\text{pooled}} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$$

$$r_{Y\lambda} = d / \rightarrow \textit{square root (}d^2 + 4)$$

M1= means for group 1 = 29.72±3.46

M2= means for group 2 = 25.30 ±3.11

The resultant value for 2 sided test for alpha = 0.05, with power = 0.80, is a sample size of 9 for each group. The formula for calculation of the sample size is set out in Box 1 and for this study produced:

$$n = 2\frac{[(a + b)^2\sigma^2)]}{(\mu_1 - \mu_2)^2}$$

$$n = \frac{2[(1.96 + 0.842)^2\ 3.285^2)]}{(29.72-25.3)^2}$$

$$N = \frac{2[(2.802)^2\ 3.285^2)]}{19.5364} = \frac{2[7.8512 \times 10.7912]}{19.5364} = \frac{2\ [84.7239]}{19.5364} = \frac{169.448}{19.5364} = \mathbf{8.67}$$

9 participants per group.

Box 1: Formula for a continuous outcome and equal sample sizes in both groups, assuming: alpha = 0.05 and power = 0.80 (beta = 0.20)

n = the sample size in each of the groups
μ_1 = population mean in treatment Group 1
μ_2 = population mean in treatment Group 2
$\mu_1 - \mu_2$ = the difference the investigator wishes to detect
σ^2 = population variance (SD)
a = conventional multiplier for alpha = 0.05
b = conventional multiplier for power = 0.80

$$n = \frac{2\,[(a+b)^2\sigma^2]}{(\mu_1-\mu_2)^2}$$

Allowing for 50% loss to follow-up, based on these calculations, a sample size of 28 participants for both groups will be needed in the pilot trial phase to ensure an adequate response rate for statistical analysis.

9. STATISTICAL ANALYSIS PLAN

Phase one: Questionnaire data will be analysed using descriptive statistics to illustrate the patients' baseline characteristics. Data will be entered into an Excel spread sheet, checked and cleaned prior to being entered into SPSS for Windows version 23. The mean will be used to assess the values of medication adherence, medication adherence self-efficacy, and beliefs about medication. The amount of variation or dispersion of data values will be quantified using standard deviation (SD) to demonstrate how close these values lie from their Means. Bivariate analyses will be conducted, examining factors potentially associated with medication non-adherence.

Logistic regression will be used to investigate factors and behaviours predictive of medications non-adherence. Two sided *p* values less than .05 will be considered to indicate statistical significance.

Phase two: Data collection and analysis will be conducted simultaneously to build on emerging themes (Polit and Beck, 2014). An inductive approach will be applied to the data, based on thematic analysis to analyse interview transcripts (Sim, 1998). This approach will focus on identifying, analysing and reporting recurrent patterns (themes) and subcategories within the data (Liamputtong, 2013). This method will examine and compare data to identify similarities and differences by reading carefully through each transcript and searching across the data set (Liamputtong, 2013, Polit and Beck, 2014). The coding process will use QSR NVivo to analyse interviews data. Thematic analysis will be conducted in six steps (Braun and Clarke, 2006).

1. **Familiarity with the data**: Transcribing the verbal data into written format entails close and extensive reading and inserting notes into transcribed material where appropriate.
2. **Generated codes**: Creating codes will arrange the data into meaningful groups.
3. **Searching for themes:** All relevant coded data will be extracted and grouped into initial sub-themes. Main themes covering sub-themes will be developed in order to address the research questions.
4. **Reviewing themes**: When all themes and sub-themes are entered, the next step is to look for common categories or themes across the entries for each question to form a coherent pattern. If some entries seem inconsistent for their category, the candidate themes will be re-categorised to find themes that adequately capture the contours of coded data. Next, the full data set is re-read to examine data relative to the themes, coding any supplementary data within themes if not coded in the first stage.
5. **Defining and naming themes**: After categorising and organising the data and themes, themes will be further determined and refined by defined titles that capture the full sense and essence of each single theme (Braun and Clarke, 2006).
6. **Writing a report**: Once interview findings are organised in the synthesised format or thematic map, they will be ready for presentation. Ultimately, the researcher will write a report including data extracts to provide a concise, coherent, logical, non-repetitive and interesting account of the

story the data tell within and across themes. Next, these extracts will be embedded within an analytic narrative that needs to go beyond description of the data to compellingly illustrate the research questions and their relationship to the argument and whether the argument has been completely answered. The study questions will be addressed by analysing the finding from quantitative phase to inform qualitative findings by developing an interpretation to merge the data and find the relationship between the quantitative results and the qualitative argument.

7. In the short term data that will emerge from qualitative analysis can reveal critical insights to inform development, translation, and dissemination of interventions to improve medication adherence behaviours.

If the researcher finds any contradiction between survey and interview responses, the participant will be asked to consider their responses and confirm which answer to take into account to ascertain if the patients is eligible for the trial phase.

Pilot trial phase: The researcher will compare the two groups at baseline. Data will be analysed according to intention to treat analysis using statistical methods based on the study hypothesis. The primary outcome will be medication adherence/non-adherence at six months and changes in adherence scores since baseline. Descriptive statistical analyses will be used to illustrate the participants' baseline characteristics. The independent samples t-test will be used to compare the mean medication adherence questionnaire scores (MSSS, MAQ, ARMS, BaMQ, and MASER-R) between the intervention and usual care groups. Paired samples t-test analysis will be used to test within groups differences on medication adherence questionnaire scores (MSSS, MAQ, ARMS, BaMQ, and MASER-R). Logistic regression analysis will be applied to identify variables that significantly influence adherence to medications (i.e. self-efficacy, beliefs, level of confidence, and social support).

10. STORAGE AND ARCHIVING OF STUDY DOCUMENTS

Electronic data will be password protected and kept on the researcher's university laptop as well as the Oxygen Cloud storage platform at UTS which will be provided further security to research data. The completed study questionnaires and materials will be secured at UTS for five years after the completion of the study and they will then be the agreed process destroyed by the Faculty of Health.

11. ETHICAL CONSIDERATIONS

The identities of the participants will be concealed to maintain their privacy and confidentiality (Liamputtong, 2013). Data will be protected by limiting access to the data to the researcher and supervisors only. The researcher will remind participants that their participation in the study will be on voluntary basis and they can withdraw from the study at any time without any consequences.

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APPENDICES

Appendix (A) Medication Adherence Questionnaires

Situations come up that make it difficult for people to take their medications as prescribed by their doctors. Below is a list of such situations. We want to know your opinion about taking your cardiac medication(s) under each of them. Please indicate your response by checking the box that most closely represents your opinion.

Questions	Yes	No
1. Do you ever forget to take your medicine?		
2. Are you careless at times about taking your medicine?		
3. When you feel better do you sometimes stop taking your medicine?		
4. Sometimes if you feel worse when you take your medicine, do you stop taking it?		

Questions	None of the time	Some of the time	Most the time	All the time
5. How often do you forget to take your medicine				
6. How often do you decide not to take your medicine?				
7. How often do you forget to get prescriptions filled				
8. How often do you run out of medicine?				

9. How often do you skip a dose of your medicine before you go to the doctor?				
10. How often do you miss taking you medicine when you feel better?				
11. How often do you miss taking your medicine when you feel sick?				
12. How often do you miss taking your medicine when you are careless?				
13. How often do you change the dose of your medicines to suit your needs (like when you take more or less pill than you're supposed to)?				
14. How often do you forget to take your medicine when you are supposed to take it more than once a day?				
15. How often do you put off refilling your medicines because they cost too much money?				
16. How often do you plan ahead and refill your medicines before they run out				

There are no right or wrong answers. For each of the situations listed below, please rate how sure you are that you can take your cardiac medications all of the time.

How confident are you that you can take your cardiac medications:	**Not at all sure**	**A little sure**	**Fairly sure**	**Extremely sure**
17. When you're busy at home				
18. When there is no one to remind you				
19. When you worry about taking them for the rest of your life				
20. When you do not have any symptoms				
21. When you are with family members				
22. When you are in a public place				
23. When the time to take them is between your meals				
24. When you are travelling				
25. When you take them more than once a day				
26. When you have other medications to take				
27. When you feel well				

28. If they make you want to urinate while away from home				
Please rate how sure you are that you can carry out the following task:				
29. Make taking your medications part of your routine				

There are no right or wrong answers. For each of the beliefs listed below, please rate how you agree or disagree about your beliefs of taking medications.

Items	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
30. My health, at present, depends on my medicines					
31. My medicines protect me from becoming worse					
32. My medicines disrupt my life					
33. I sometimes worry about long-term effects of my medicines					
34. Doctors use too many medicines					
35. People who take medicines should stop their treatment for a while every now and again					
36. Most medicines are addictive					
37. Medicines do more harm than good					

For the next set of questions, please indicate how often people may have helped you in the various ways described during the PAST THREE MONTHS.

How often has someone in the past three months?

Questions	Never	Rarely	Sometimes	Often	Very often
38. Helped you monitor your symptoms and medication side effects?					
39. Reminded you to take your medications?					
40. Picked up your cardiac medication prescriptions for you?					
41. Helped you understand information about your medications?					
42. Checked in with you about your medications?					
43. Encouraged you to talk to your doctor about your medications when you have questions or problems?					
44. Helped you to believe you can take your medications as prescribed?					
45. Called you specifically to ask how you were doing with your cardiac medications?					

Appendix (B) Data Collection Sheet

Appendix (B) Data Collection Sheet

Age: _____ years **Gender**: Male □ Female □

DEMOGRAPHIC DETAILS: (Patient Questions)

Employment Status:

Employed □ Unemployed but seeking work □

Retired □ Unemployed and not seeking work □

Living Arrangement: Lives alone □ With partner □

With Family or Carer □ With other □

Marital Status: Married □ Widowed □ De facto □
Divorced □ Single □ Separated □

Social background: ----------**Ethnicity/Country of birth** ----------
-

Education: years of full time education completed ---------- years.

Diseases you have been diagnosed with (Put a X in the box for those that apply to you):

Diabetes Mellitus □ Respiratory disease □ Renal diseases □

Others (please list): ----------

Patient's name: ----------

Postcode: ----------

Preferred phone number: ----------

Email: ----------

Preferred interview days: ---------- Times: ----------

Cardiac medications:

Drug 1: type ---------- Dosage ----------

Number of pills to be taken: ---------- Times ----------

Drug 2: type ---------- Dosage ----------

Number of pills to be taken: ---------- Times ----------

Drug 3: type ---------- Dosage ----------

Number of pills to be taken: ---------- Times ----------

Drug 4: type ---------- Dosage ----------

Number of pills to be taken: ---------- Times ----------

Drug 5: type ---------- Dosage ----------

Number of pills to be taken: ---------- Times ----------

Appendix (C): Semi-Structured Interview Guide

Time:…….. **Date**:…….
Location:……... **Name Symbol:** …….

Introduction:

Thank you for agreeing to participate in this interview and we will be happy and look forward to your participation till the end of this study.

You are invited to participate in a study being undertaken by Ali Al-Ganmi (a nursing doctoral student at University of Technology Sydney (UTS)) and supervised by Professor Lin Perry (Prince of Wales Hospital and UTS) and Dr. Leila Gholizadeh (UTS).

This study looks at how patients with heart disease manage their medications. We are undertaking this study because reports show that for many reasons a significant number of people do not take their medicines in the way they have been prescribed. On average only 50% of medications are taken as prescribed and this is a risk for people health. We want to see if we can help people who have trouble with taking their medications as they have been prescribed.

The interview:

- This should take no more than 60 minutes of your time.
- I would like to ask you some questions about your personal experiences with taking medicines as a heart patient in cardiac rehabilitation.
- I am aware that you were referred to this cardiac rehabilitation program after your heart event and you have now been prescribed heart medicines.
- I would like to ask you some questions about your experiences with taking your medicines.

● There are no right or wrong answers. I just want to know what you think. If there are any questions that you prefer not to answer, please feel free to say so. Anything we discuss will be completely confidential.

● I would like to tape record this interview, and then type up what we talk about into a computer. This will be just so I don't miss anything. Your name or any other identifying information will be removed. We will destroy the audiotape once our conversation has been typed up. Anything you say will be combined with other people's interviews and summarized. Your actual words may be used, but you will not be identifiable. Is this agreeable to you?

● You can withdraw at any time from any part of the study without affecting your participation in previously completed parts of the study.

Interview Questions:

- **What medications or medicines are you currently on?**

  (Prompts: If you can't remember the name, can you remember what they are for? OR – why do you take each of these? Can you tell me what they are for? If not can I remind you of them by reviewing your discharge letter?**)**

- **Have you taken them today?**

  (Prompts: What time do you usually take each of your medications/ tablets/ pills?**)**

- **How do you feel about your prescribed heart medicines?**

  (Prompts: Are you feel better when you take your medications (For example, have no chest pain, breathing difficulties)? OR – Do you think taking medications makes you feel worse?, If so, why is that?**)**.

- **How do you find taking your prescribed heart medicines? Why?**

  (Prompts: What make you decide to take your medications? (Pain symptoms) OR What happens when you take- or don't take – your medicines? Does anything change? If so, What make you stop take your medications? (Side effects, not have

symptoms, between your meals, traveling, many medication are a lot for you, make you want to urinate**)**.

- **Do you find any difficulties with taking your medicines in the way they are prescribed for you? Can you tell me about this?**

  (Prompts: medication name (generic or trade), number of medications, physical disability, forgotten, careless at times, distance, time constraints**)**.

- **What strategies do you use to help you take your medications as the way they are prescribed for you?**

  (Prompts: Do you booked a visit with your GP or cardiac specialist to discuss about you medication? You talk with other patients about cardiac medications? Staff explain how you can use your medications?**).**

- **Is there anything that you think might make it easier for you to take your medicines the way they were prescribed for you? If yes –what are these?**

  (Prompts: Specific method you use to remind you taking medicine? Your family member, friends, hospital staff? Your physician, pharmacist, nurse?).

- **Please describe your experience refilling your medications. How easy is it for you to get your medications refilled? If not, tell me why?**

  (Prompts: Did you have any body remind you to go and refill your medicines? Do you have someone who helps you to remember to take your tablets? If yes: Do you rely on them completely to remind you to take your tablets or is it mostly your job to remember and take your tablets?).

Thank you for your time. It is greatly appreciated.

Appendix (D): An Example of a Motivational Interviewing (MINT) for a Standard Cardiac Patient

Time:…….. **Date**:……

Location:…… **Name Symbol:** ……

Introduction:

Thank you for agreeing to participate in this motivational interview.

You are invited to participate in this trial phase because you have already take part in phase one survey and phase two (interview). All patients who complete the survey and the interview and have medications adherence difficulties and a factors affected their medication adherence will be eligible to participate in this motivational interview.

The interview:

● This should take no more than 40 minutes of your time.

● We are going to talk about your personal experiences with taking medicines as a heart patient in cardiac rehabilitation.

● I would like to discuss with you some questions about your experiences with taking your medicines.

● I would like to tape record this interview, and then type up what we talk about into a computer. This will be just so I don't miss anything. Your name or any other identifying information will be removed. We will destroy the audiotape once our conversation has been typed up. Anything you say will be combined with other people's interviews and summarized. Your actual words may be used, but you will not be identifiable. Is this agreeable to you?

Example of Motivational interviewing interaction

- Did you have any concerns or anything you would like to talk about before looking at results of your answers in the survey? If yes, tell me about it?
- What I would like to do is talk with you about work or doesn't work for you. I am here to support you in your efforts to anything prevent you from taking your medicines as prescribed.
- There is a benefit of taking your medicines as prescribed for you.
- We have your survey results here and I wondering if you would like to review that with me.
- Would you like me to explain them for you?
- Your survey results suggest you have a low level of medication adherence and there are some factors affecting how you take your medications, what are your thoughts about that?
- You believe that all long-term medicines that are prescribed for you have side effects and disturb your life, and you cannot tolerate it anymore.
- You believe that medicines that are prescribed for you will not benefit your health and will harm you. So, if you stop take them, does your health improve?
- On one hand, you know what you need to do differently to improve your health by taking your medicines at the time prescribed for you to decrease your heart

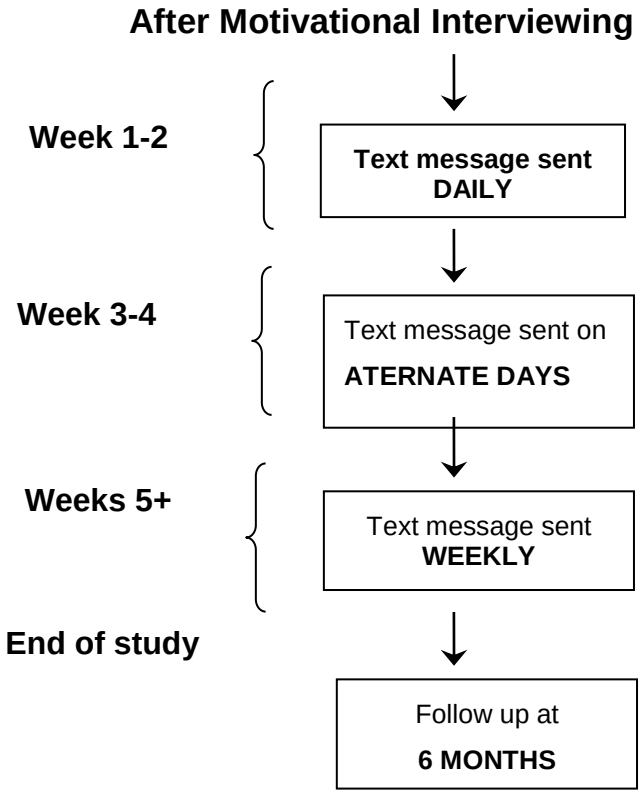
disease risks. On the other hand, you are overwhelmed by many other things in your life and are working on taking medicines as prescribed a little at a time because you want to improve your health.

- You should be proud of all effort you have put into taking your medicines as prescribed and the changes you have made in medication adherence. Small steps are what bring us to rewards in the end.

- I am confident that as you continue to set small goals for yourself, you will accomplish them and find good strategies for taking your medicines as prescribed that works for you.

Thank you for your time. It is greatly appreciated.

Appendix (E): The text message (TM) reminder content



Text message reminders (TM) will be sent to these participants one text message daily for two weeks, then alternate day texts for two weeks and then weekly texts for the next 6 months. The content of the text message reminders will vary according to the patients' non-adherence factors. An example of the text message reminder is:

'Hello Mr/Mrs……. Have you refilled your heart medication today? Please text back "Y" if your answer is "Yes, I have refilled my medication before receiving this text", "R" if your answer is "the message has reminded me, I will refill my medication" and "N" if your answer is "No". Thank you. Ali.

Non-responders or patients who reply back 'No' in response to the message will receive a telephone call from the researcher, to determine whether the patient is experiencing problems taking or refilling their medication, and resolve this if possible (e.g. the patients has difficulty accessing the pharmacy). If the patient mentioned experiencing side-effects from medications, the researcher will advise the patient to make an appointment with their GP or consulted with their pharmacist. If researcher cannot contact the patient by telephone, a letter will be sent to their home address informing them that the researcher has been unable to contact them by telephone and asking them to contact the study team.