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TEXT messages to improve MEDication adherence and Secondary prevention (TEXTMEDS) after acute coronary syndrome: a randomised clinical trial protocol.

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Title: TEXT messages to improve MEDication adherence and Secondary prevention (TEXTMEDS) after acute coronary syndrome: a randomised clinical trial protocol.

Short Title: Text messages to improve medication adherence and prevention following a cardiovascular event (TEXTMEDS)

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ABSTRACT

Background: Identifying simple, low-cost and scalable means of supporting lifestyle change and medication adherence for patients following a cardiovascular event is important. **Objective:** The TEXTMEDS study aims to investigate whether a cardiac education and support program sent via mobile phone text message improves medication adherence and risk factor levels in patients following an acute coronary syndrome (ACS).

Study design: A single blind, multicentre, randomised clinical trial of 1400 patients after an ACS with 12 months follow-up. The intervention group will receive multiple weekly text messages that provide information, motivation, support to adhere to medications, quit smoking (if relevant), and recommendations for healthy diet and exercise. The primary endpoint is the percentage of patients who are adherent to cardioprotective medications and the key secondary outcomes are mean systolic blood pressure and LDL-cholesterol. Secondary outcomes will also include total cholesterol, mean diastolic blood pressure, the percentage of participants who are adherent to each cardioprotective medication class, the percentage of participants who achieve target levels of cardiovascular risk factors, major vascular events, hospital readmissions and all-cause mortality. The study will be augmented by formal economic and process evaluations to assess acceptability, utility and cost-effectiveness.

Summary: The study will provide multi-centre randomised trial evidence of the effects of a text-message based program on cardioprotective medication adherence and levels of cardiovascular risk factors.

Ethics and dissemination: Primary ethics approval was received from Western Sydney Local Health District Human Research Ethics Committee [HREC2012/12/4.1 (3648) AU RED HREC/13/WMEAD/15]. Results will be disseminated via peer-reviewed publications

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STRENGTHS AND LIMITATIONS OF THE STUDY

- This is a multi-centre trial that will provide the evidence for effectiveness of text messaging programs and their generalisability above existing trial evidence from single centre studies.
- The intervention development follows a previously published process, the messages are based on psychological behaviour change theory and the message management is via a custom-built computerised program.
- Alongside this study we have included an economic evaluation study and process evaluation.
- This is a study conducted across multiple centre of Australia only and uses English text only.
- The primary and key secondary study outcomes are surrogate outcomes measures and not hard clinical outcomes measures such as major adverse cardiovascular events.

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INTRODUCTION

Cardiovascular disease (CVD) is the leading burden of premature death and disease globally.(1) About half of the patients who have had a prior hospital admission for coronary heart disease (CHD) will have a recurrent event.(2) If survivors of acute coronary syndrome (ACS) attend secondary prevention programs,(3, 4) adhere to risk factor modification and are compliant with drug regimens,(5-7) their hospital readmissions within one year may be reduced and their survival improved.(8, 9)

Despite the overwhelming evidence of the effectiveness of secondary prevention programs under-written by guidelines, (10, 11) surveys from multiple countries demonstrate gaps in uptake of cardioprotective medications and lifestyle recommendations.(12, 13) The World Health Organization (WHO) report in 2003 highlighted medication non-adherence as a global concern,(14) and the World Heart Federation have identified secondary CVD prevention as a public health priority and key to achieving the WHO's target of 30 percent reduction in premature mortality from non-communicable diseases by 2030.(15)

A number of interventions can improve adherence to cardioprotective medications among patients with CHD, and simple interventions, including text-message reminders, have similar effectiveness to more complex interventions in improving adherence.(16) Text-message based interventions have gained increasing traction as a potential low-cost means of providing self-management support to patients seeking to change health behaviours. This increase has been driven by an accumulating body of research evidence(17-23) as well as the global reach of mobile phones.(24) A systematic review and meta-analysis of 16 studies of text-message-based interventions to support medication adherence among patients with chronic diseases demonstrated that text-messaging approximately doubles the odds of

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medication adherence (OR 2.11, 95% CI 1.52 – 2.93; p<0.001). There are important limitations of the current literature however, including small sample sizes (median sample size 97, range 21 – 538), significant heterogeneity and short duration follow-up (median intervention duration 12 weeks, range 4 – 48 weeks).(25)

It is in this context, that we developed the TEXT messages to improve MEDication adherence and Secondary prevention **(**TEXTMEDS) study. TEXTMEDS is a multi-centre randomised clinical trial of patients with ACS to determine the effect of a semi-personalised secondary prevention program delivered via mobile phone text messages on medication adherence, blood pressure, LDL-cholesterol and other clinical outcome measures in patients after an ACS.

METHODS AND ANALYSIS

Study Design

TEXTMEDS is a single blind, multi-centre, randomised controlled trial delivering a 12 month secondary prevention program via text messages to ACS patients (Figure 1). The recruitment sites include 15 public hospitals in urban and rural Australia that serve ethnically, culturally and socioeconomically diverse communities. The target sample size is 1400 patients with a confirmed diagnosis of ACS. Participants are randomly allocated to either control or intervention group. The control group is assigned to receive standard care as determined by their treating physician. The intervention group is allocated to receive, in addition to standard care, multiple weekly text messages that provide information, motivation and support for medication adherence, smoking cessation (if relevant), recommendations for healthy diet and exercise and other cardiac prevention advice. Trained research personnel blinded to the group allocation conduct assessments at baseline and 12 months during a face-

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to-face interview and at six months by phone. Further data will be obtained via extraction of linked data available with consent from government repositories. The study will be augmented by formal economic and process evaluations to assess acceptability, utility and cost-effectiveness of the intervention. This study will be monitored and managed centrally with periodic site monitoring visits.

Randomisation and blinding

After obtaining written informed consent, the data are entered by the site coordinator into a web-based case record form (CRF) and then randomisation occurs via a centralised, computerised randomisation program in a uniform 1:1 allocation ratio. The text message program is initiated after the patient is discharged from the hospital and the patients (but not their care providers, research personnel or investigators) are informed of their allocation through a single text message. Study coordinators and research assistants conducting the assessments and statisticians will be blinded. This randomisation program is electronically linked to the software program that delivers the text-message intervention, thereby minimising need for human interference. Key participant characteristics that determine text message customisation and personalisation are also automatically imported into software administering the intervention.

Study population

Patients with a confirmed diagnosis of ACS are eligible for the study. ACS is defined based on one of the two following criteria;

1. Acute myocardial infarction consistent with the 3rd Universal definition of MI (26): Detection of rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial

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ischemia with at least one of the following; (i) symptoms of ischemia ; (ii) ECG changes indicative of new ischemia ; (iii) development of pathological Q waves on ECG or: (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

2. Patients admitted to hospital acutely with symptoms typical of cardiac ischemia not meeting the above criteria and one of the following indicators of coronary artery disease CAD; (i) new or known coronary angiographic evidence of coronary disease (coronary artery narrowing of ≥ 50% of at least one major vessel) or: (ii) prior coronary artery bypass graft surgery or: (iii) prior percutaneous coronary intervention.

Patients must also meet the following inclusion criteria: (i) ability to provide informed consent, (ii) own an operational mobile telephone and (iii) can read text messages in English on a mobile phone, (iv) life expectancy greater than six months. For those people who are ineligible or decline to participate, a 'screening log' of basic demographic information and reasons for non-participation is maintained.

Control group

The control group will receive standard care post-ACS as determined by their usual doctors. This generally includes secondary prevention cardiovascular medications and referral to a centre-based cardiac rehabilitation or other secondary prevention program.

Intervention

The intervention group will receive standard care (as described above), plus an additional support package that includes a series of text messages focusing on medication adherence and

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lifestyle modification as well as an opportunity to communicate with an English-speaking health counsellor over a 12-month period as detailed below.

Message content, frequency, sequence

The text message intervention builds upon our previous experience in developing text-message interventions from the TEXT ME study.(17) We have previously described the process of message content development,(27) as well as the details of the intervention and its delivery, including the similarities and differences of the TEXT ME and TEXTMEDS study in a separate manuscript.(28) For TEXTMEDS, the majority of text messages providing information and support on lifestyle modification are from the TEXT ME study,(17) and in addition, participants receive weekly support from a bank of text messages we developed with a focus on cardiovascular secondary preventative medications and barriers/ enablers to medication adherence.(29, 30) This included information about the drug's mechanism of action, research evidence as well as common side effects, and provided motivation, including tips and reminders to improve medication adherence. The program is structured such that education on medications is suitable for low health literacy at the start and increases in complexity during the course of the program. Each participant receives a customised and personalised set of messages (Box 1). Thus messages are 'customised' by selecting content relevant to participant characteristics such as medication class prescription, dietary habits (vegetarian or non-vegetarian) and/ or smoking status. Messages are 'personalised' as the preferred name of the participant is incorporated into some messages using a mail-merge type of function. Participants receive two to four messages per week, receiving fewer messages during mid-study. The messages will be sent at random working hours on random weekdays. Each message will have a unique signature (study and hospital name) to ensure that participants know these messages are from the TEXTMEDS study and participants at

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baseline will be given a brief training on how to read, delete and save a text message and unsubscribe if required. Participants can also update their key information – e.g. mobile phone number, change in smoking status or types of medications through the course of the study and this will be reflected in the ongoing text messages they receive. Messages are sent at no cost to the participants and a bulk-rate cost to the study. Differently to the TEXT ME study,(17) the TEXTMEDS intervention was designed to encourage two-way communication. Thus, once a month, participants allocated to the intervention are sent a message encouraging them to text the health counsellor to ask questions or request additional information.

Role of the Health Counsellor

A health counsellor located at the coordinating centre monitors and responds to participants' replies from across Australia either via text message or phone call within three working days.(28) The health counsellor has health professional qualifications (e.g. nurse or dietitian) and is given specific training to respond to patients' requests and provide further guidance using an intervention manual we have developed for the study. The health counsellor is assisted as required by a clinical research fellow (cardiologist or cardiology sub-specialty trainee and clinicians from the study investigator team). All replies and responses are reviewed in regular weekly team meetings.

Message management system

The TEXTMEDS message management system is a more sophisticated version of the original TEXT ME software program used to deliver the TEXT ME intervention. In brief, it uses a web interface to enable the simultaneous entry of data from multiple study centres. Key participant characteristics are automatically imported from electronic databases into the

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software administering the intervention to customise and personalise messages. The program is configured to run a series of background checks to ensure data accuracy, integrity and system functioning. A detailed log of all transactions with participants, including delivery reports, participants' replies and health counsellor's interactions is maintained.

BOX 1: Examples of text messages sent to the intervention group(27, 31)
Introductory message Hi <NAME>, Welcome to TEXTMEDS. We hope you enjoy the messages. If you have received this in error respond STOP to opt out. TEXTMEDS <NAME> Hospital.
Medication-related messages Hi <NAME> are you still taking your medications every day? Keep it up! Aspirin stops the blood platelets from sticking & prevents blood clots forming <NAME> take aspirin once per day with food. You may be on Angiotensin Receptor Blockers (names end in artan) they help lower BP Remember _ cholesterol & blood pressure lowering tablets need to be taken every day
Lifestyle-related messages Check out www.heartfoundation.org.au for tips & info about preventing heart disease Hi <NAME>, why not try and use the stairs instead of the lift Try steaming, baking or BBQ to reduce the need for excess oil when cooking <NAME>, try identifying the triggers that make you want a cigarette & avoid them
Two-way communication messages Do you have any questions for our health counsellor <NAME>? Text us your question and we will contact you shortly.
Final message

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This is your last message from TEXTMEDS. Best wishes from ALL of us. We hope that you enjoyed the messages over the past 12months.

BBQ, Barbeque; BP, blood pressure

Data collection and study outcomes

The follow-up study assessments will occur at six months by phone and 12 months in-person. The primary outcome of medication adherence to cardioprotective messages will be the difference between intervention and control groups in the percentage of patients adherent to all five classes of recommended cardioprotective medications (unless contraindicated/previously documented intolerance). The five cardioprotective classes of medications are: 1) angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blockers (ARBs), 2) beta-blocker, 3) statin lipid-lowering, 4) aspirin and 5) adenosine diphosphate (ADP) receptor antagonist. Medication adherence will be measured by asking participants on how many days in the past 30 days they missed a particular class of medication for each of the five classes of medications indicated and this is asked at both six and 12 month visits. Patients will be defined as adherent if they report that they have taken their indicated medications on >80% of days (>24/30 days) at both six and 12 month visits.(19) Indicated medications will be all five classes of guideline recommended medications listed above unless a contra-indication is documented in their case report forms.

The key secondary outcomes are the difference between intervention and control groups at 12 months for LDL-cholesterol level and systolic blood pressure (raised blood pressure). Other secondary outcomes include: total cholesterol, diastolic blood pressure, the proportion of participants adherent to each medication class, other cardiovascular risk factors including behavioural risk factors, psychosocial factors, major cardiovascular events, hospital readmissions and all-cause mortality and composites of risk factor control and major adverse

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cardiovascular events (MACE) (Table 1). A formal endpoint adjudication process will be implemented and includes revision all original documents of the major cardiovascular events, hospital readmissions and deaths by two independent adjudicators. The adjudication process is overseen by KS. Serious Adverse Events will be collected by the investigator/ research coordinator from randomization to 30 days after the end-of-study visit and reported to the central coordinating centre as well as to ethics as per local guidelines. To optimise follow-up, multiple attempts will be made to contact participants including contacting their referring doctor and at a minimum we will aim to record vital status for all participants.

Data management is via a secure clinical trial data management system managed by TGI with data entry through a password protected, web-based interface by registered staff, real-time data query generation for values entered outside of pre-set valid ranges and consistency checking. The steering committee (chaired by CC) has the overall responsibility for execution of the study.

Table 1: Study outcomes

Outcome	Assessment	Baseline	6-month	12-month
Primary outcome				
Medication adherence	Proportion of patients that are adherent to five out of five indicated medications (or four of four, if five not indicated). Adherence defined as taking medications on > 24/30 days for all		✓	✓

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	medicines at two time points of 6, 12 months.(19)			
Key secondary outcomes				
Systolic BP	Average of two resting, sitting digital recordings	✓		✓
LDL-cholesterol	Fasting blood sample	✓		✓
Secondary outcomes				
Medication adherence	Proportion of patients adherent to the separate drug classes		✓	✓
Diastolic BP	Average of two resting, sitting digital recordings	✓		✓
Total-cholesterol	Fasting blood sample	✓		✓
Smoking	Self-report	✓		✓
Obesity	Weight, height, waist and hip circumference	✓		✓
Physical activity	*General Physical Activity Questionnaire(32)*	✓		✓
Fruit and vegetable intake	*WHO Steps instrument(33)*	✓		✓
Anxiety symptoms	Generalized Anxiety Disorder 7-item (GAD-7) scale(34)			✓

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Depressive symptoms	Patient Health Questionnaire (PHQ-9)(35)			✓
Quality of life	*SF-12_V2™ Health Survey(36)*	✓		✓
CV events	CV death, non-fatal AMI, stroke or hospital admission with unstable angina or congestive heart failure		✓	✓
All-cause mortality	Data linkage		✓	✓

AMI, Acute myocardial infarction; BP, blood pressure; CV, cardiovascular; LDL, Low-density lipoprotein; WHO, World Health Organization

Process measures

Process evaluations explore the implementation, receipt, and setting of an intervention and assist in the interpretation of outcome results.(37) Analyses will be informed by the Pawson and Tilley realistic evaluation model,(38) which is an approach grounded in realism that considers social, individual, contextual and material contributions to change. We will use mixed methods to investigate why the TEXTMEDS strategy may or may not have been effective and which intervention components were most influential.

The process evaluation will include a semi-quantitative survey and focus groups with intervention participants. All participants receiving the intervention will be invited to complete a written questionnaire assessing their perceptions, experience and the degree of engagement with the intervention at the completion of the trial. The questionnaire will comprise a combination of closed 5-point Likert scale and open questions. A sample of the intervention group participants will be invited to participate in focus groups on perceptions of

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the utility and acceptability of the intervention program. To obtain a broad range of views we will use a maximum variation sampling method based on patient characteristics such as gender and site. Sampling will continue until thematic saturation is reached however, we anticipate approximately four focus groups will be needed. An in-depth interview will also be conducted with the health counsellor to understand his/her perceptions of patients' engagement with the program. Focus groups and the health counsellor interview will be conducted by a trained qualitative interviewer, digitally recorded and transcribed. Analyses will be thematic and coding based on emergent themes.

Economic analysis

The costs and health outcomes associated with the intervention will be compared in an incremental cost-effectiveness analysis. A health sector perspective will be adopted. The costs of delivering the intervention will be assessed by measuring and valuing the incremental resources used.(39) Hospitalisations will be collected at each follow-up. Consent will be sought for access to individual participant Medical Benefits Schedule and Pharmaceutical Benefits Scheme claims usage through Medicare Australia to ascertain use of medical services and prescribed pharmaceuticals. Changes to health benefits will be assessed using Quality Adjusted Life Years (QALYs). These will be assessed using the SF-12_V2™ Health Survey(36) (License Number QM024287). Although we do not expect significant differences in survival or quality of life between treatment groups within trial, these data are needed to provide an estimate of the baseline quality of life in this patient population. Given the likely small numbers of cardiovascular events occurring within the trial, the quality of life and costs data collected *in-trial* will need to be modelled using data on quality of life and cost associated with cardiovascular events from literature review.(40) Long terms costs and QALYs will be modelled using a decision analytic Markov model that will enable us to

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extrapolate beyond the data collection period, predict within the cohort the occurrence of cardiovascular events over a lifetime and thus estimate longer term costs, potential cost savings and benefits of the intervention.(41)

Statistical considerations

A 10% improvement in the proportion taking appropriate secondary prevention is considered to be a clinically meaningful increase and associated with a decrease in short-term mortality.(42) To test for a 10% improvement in the primary outcome (RR of 1.10) in the treatment compared to the control arm (assuming ~70% of patients are taking appropriate secondary prevention in control arm, based on contemporary Australian registry data,(43, 44) and this would rise to 77% in the intervention arm) with 80% power (type I error = 5%, two-sided test), we would require a total sample size of 1246, rising to ~ 1396 accounting for a ~10% loss to follow up. This sample size of 1246 would enable us to also detect with 80% power a minimum detectable difference in secondary outcomes of i) 0.15 mmol/L in LDL-cholesterol assuming a standard deviation (SD) of 0.92mmol/L,(45) ii) 2.7 mmHg in systolic blood pressure, assuming a SD of 17mmHg(45) and a minimum detectable relative risk of 0.69 in CV events assuming a major CV event rate of 19% or a power of approximately 13% to detect a relative risk of 0.80 in CV events, assuming a lower CV event rate of 5% at 12 months from contemporary Austalian data.

The intention to treat principle will be used and patients will be analyzed according to the group to which they are allocated. A detailed statistical analysis plan will be prepared prior to the analysis. The primary outcome will be compared between groups using the chi-square test. The primary analysis will be unadjusted. The mean level of blood pressure and cholesterol will be analyzed using an analysis of covariance using the baseline values as the

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covariate with estimation of the mean difference and corresponding 95% CI. For each of the secondary outcome measures, parameters will be compared between the two groups with relevant statistical tests providing mean difference for continuous variables or relative risks for dichotomous variables along with the 95% confidence intervals and two-sided p-values.

We will also analyze effects across subgroups, such as sex and age, using logistic regression models with treatment group, subgroup and subgroup by treatment interaction as fixed effects. Number of patients with major cardiovascular events will be compared between treatments using a chi-square test. The criterion for statistical significance will be set at $\alpha = 0.05$. Number needed to treat (NNT) will also be calculated and its 95% CI for the primary outcome.

ETHICS AND DISSEMINATION

The findings of this study will be disseminated via the usual scientific forums including peer-reviewed publications and presentations at international conferences. The study is sponsored by The George Institute for Global Health at the University of Sydney, and centrally coordinated and managed by staff based mainly at Westmead Hospital and the George Institute. The design and conduct of the study is overseen by a Steering Committee (authors and some site principle investigators). This committee has expertise in large-scale clinical trials and qualitative research, economic analysis, clinical cardiovascular disease management and healthy policy implementation. This study will adhere to the Australian National Health and Medical Research Council ethical guidelines for human research. Formal ethical approval for this study has been obtained from Western Sydney Local Health District Human Research Ethics Committee [HREC2012/12/4.1 (3648) AU RED HREC/13/WMEAD/15]. The current protocol is version 3.0 (31 October 2013). Any changes in the protocol during the trial that may affect the conduct of the trial, safety, and the benefit to

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patients will require a formal amendment to the protocol. Written and informed consent will be obtained from all participants.

DISCUSSION AND CONCLUSION

The TEXTMEDS study will evaluate an innovative means of delivering a cardiac prevention program to survivors of an ACS event and whether it improves important cardiac prevention targets in this patient population including medication adherence and risk factor levels. While text-message based programs are not new, what makes them innovative in the space of cardiac prevention is their now massive reach, given that mobile phone ownership approaches 100% in many countries and they all receive text.

The focus of this study on medication adherence is due to its very large and important role as a component of post-ACS prevention. Improving medical adherence to cardioprotective medicines has been shown to reduce cardiovascular morbidity and mortality. One challenge however in this area, is the optimal means of measuring medical adherence. There are no gold standard measures of adherence and self-reported measures are the most well-accepted and practical means of measuring adherence in clinical trials. We acknowledge that self-reported measures can overestimate adherence, but this should not impact the difference in adherence between the intervention and control groups. To get an objective measure of the impact of the intervention, key outcomes for this trial will also be LDL-cholesterol and blood pressure, which are both strong and objective measures of cardiovascular risk. We will also be examining the impact of the intervention program on behavioural risk factors, which our predecessor study to this, TEXT ME, demonstrated a substantial impact.

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In our previous single-centre study – TEXT ME, our group has demonstrated that a lifestyle-focused text-messaging program was associated with reductions in LDL-cholesterol, blood pressure, body mass index (BMI) and smoking, and with increases of physical activity levels. TEXT ME also demonstrated that participants in the intervention group were more likely to achieve risk factor control for multiple risk factors with 28.9% in the intervention, versus 10.3% in the control group achieving target levels of 4 or more key risk factors (RR 2.80, 95% CI, 1.95 – 4.02).(17) The TEXTMEDS study will extend the knowledge from the TEXT ME study by examining the impact of a longer text-message program (12 months versus six months) and delivered across multiple urban and rural hospitals in a range of socioeconomically varied contexts across the breadth of Australia. By involving a health counsellor to track and respond to messages, TEXTMEDS will also provide information on whether interactivity is regarded as important by participants.

A cardiac prevention program delivered via text messages has the advantages of low cost and being easily automated. These elements can allow these programs to reach large numbers of people, including those in resource-poor settings and in geographically isolated communities, and therefore, the potential to have a substantial population impact.

In conclusion, the TEXTMEDS study will provide multi-centre randomised controlled data on whether a cardiac prevention program delivered to support cardiac prevention across multiple hospital sites is of utility and effective in improving targets of cardiac prevention in patients post- ACS.

REPORTING AND DISSEMINATION

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Results of this study will be presented at national meetings and published in a scientific journal. Participants will not be individually notified regarding the results of this study.

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AUTHOR'S CONTRIBUTIONS

CC had the original idea. JR, AT, DB, GH, AR, SJ, DC were involved in study design and protocol development. SS and LB contributed to the design of the statistical analysis approach. KS, CK, JT, RJ, KR, were involved in literature review and developing study instruments and materials. JA, RB, NC, SC, CHC, NK, AM, MM, PS, PT are site PI involved in providing a critical review of the manuscript. All authors read and approved the final manuscript

COMPETING INTERESTS

The authors declare they have no competing interests.

FUNDING

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ROLE OF THE FUNDING SOURCE

The organisations that supported this work (through peer-reviewed, educational research grants) had no role in study conception, data collection, analysis and interpretation, and writing of the manuscript.

DATA SHARING STATEMENT

This is a pre-results trial protocol publication.

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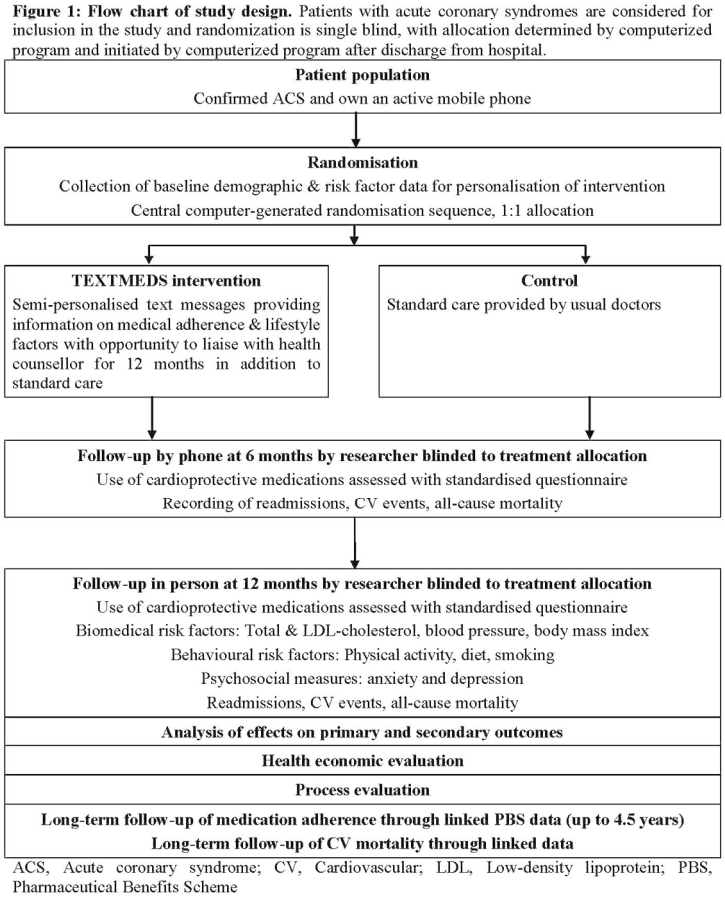

Figure 1: Flow chart of study design. Patients with acute coronary syndromes are considered for inclusion in the study and randomization is single blind, with allocation determined by computerized program and initiated by computerized program after discharge from hospital.

210x297mm (200 x 200 DPI)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____page 1____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___page 4____
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a____
Protocol version	3	Date and version identifier:	__page 19____
Funding	4	Sources and types of financial, material, and other support	___page 22_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___page 1 & 21_
	5b	Name and contact information for the trial sponsor	See ethics approval letter
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____page 22___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____page 14__
Introduction			

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Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____page 5_
	6b	Explanation for choice of comparators	____page 9_
Objectives	7	Specific objectives or hypotheses	____page 7_
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____page 7__
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____page 8___
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___page 8____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___page 9____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_not a drug trial_
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	not a drug trial_
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__page 9_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__page 13_
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___figure 1____

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___page 17_
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___n/a_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___page 8____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__page 8____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__page 8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__page 8_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__page 8____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___page 13____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___page 14___

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___page 14___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___page 18___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___page 18__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___page 18___
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___page 14__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__page 18__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__page 14_
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____n/a_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____page 19___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____page 19__

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___page 19___
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___page 17____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___page 13-14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___page 22____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___page 23___
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	The intervention = text messages
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___page 22___
	31b	Authorship eligibility guidelines and any intended use of professional writers	____page 22___
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___no plans_
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__attached___
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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