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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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ABSTRACT

Background Identifying simple, low-cost and scalable means of supporting lifestyle change and medication adherence for patients following a cardiovascular (CV) event is important.

Objective The TEXTMEDS (TEXT messages to improve MEDication adherence and Secondary prevention) study aims to investigate whether a cardiac education and support programme 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 (BP) and low-density lipoprotein cholesterol. Secondary outcomes will also include total cholesterol, mean diastolic BP, the percentage of participants who are adherent to each cardioprotective medication class, the percentage of participants who achieve target levels of CV 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 multicentre randomised trial evidence of the effects of a text message-based programme on cardioprotective medication adherence and levels of CV 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 and presentations at international conferences.

Strengths and limitations of this study

- This is a multicentre trial that will provide the evidence for effectiveness of text messaging programme 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 programme.
- Alongside this study, we have included an economic evaluation study and process evaluation.
- This is a study conducted across multiple centres of Australia only and uses English text only.
- The primary and key secondary study outcomes are surrogate outcome measures and not hard clinical outcome measures such as major adverse cardiovascular events.

Trial registration number ACTRN12613000793718; Pre-results.

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 programme,[3 4] adhere to risk factor modification and are compliant with drug

regimens,[5–7] their hospital readmissions within 1 year may be reduced and their survival improved.[8 9]

Despite the overwhelming evidence of the effectiveness of secondary prevention programmes underwritten by guidelines,[10 11] surveys from multiple countries demonstrate gaps in uptake of cardioprotective medications and lifestyle recommendations.[12 13] The 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 WHO's target of 30% 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 medication adherence (OR 2.11, 95% CI 1.52 to 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 multicentre randomised clinical trial of patients with ACS to determine the effect of a semipersonalised secondary prevention programme delivered via mobile phone text messages on medication adherence, blood pressure (BP), low-density lipoprotein (LDL)-cholesterol and other clinical outcome measures in patients after an ACS.

METHODS AND ANALYSIS

Study design

TEXTMEDS is a single-blind, multicentre, randomised controlled trial delivering a 12-month secondary prevention programme via text messages to patients with ACS (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-to-face interview and at 6 months over 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 programme in a uniform 1:1 allocation ratio. The text message programme 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 programme is electronically linked to the software programme 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 Third Universal definition of myocardial ischaemia (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 MI with at least one of the following: (1) symptoms of ischaemia; (2) ECG changes indicative of new ischaemia; (3) development of pathological Q waves on ECG or (4) 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 ischaemia not meeting the above criteria and one of the following indicators of coronary artery disease: (1) new or known coronary angiographic evidence of coronary disease (coronary artery narrowing of ≥50% of at least one major vessel) or (2) prior coronary artery bypass graft surgery or (3) prior percutaneous coronary intervention.

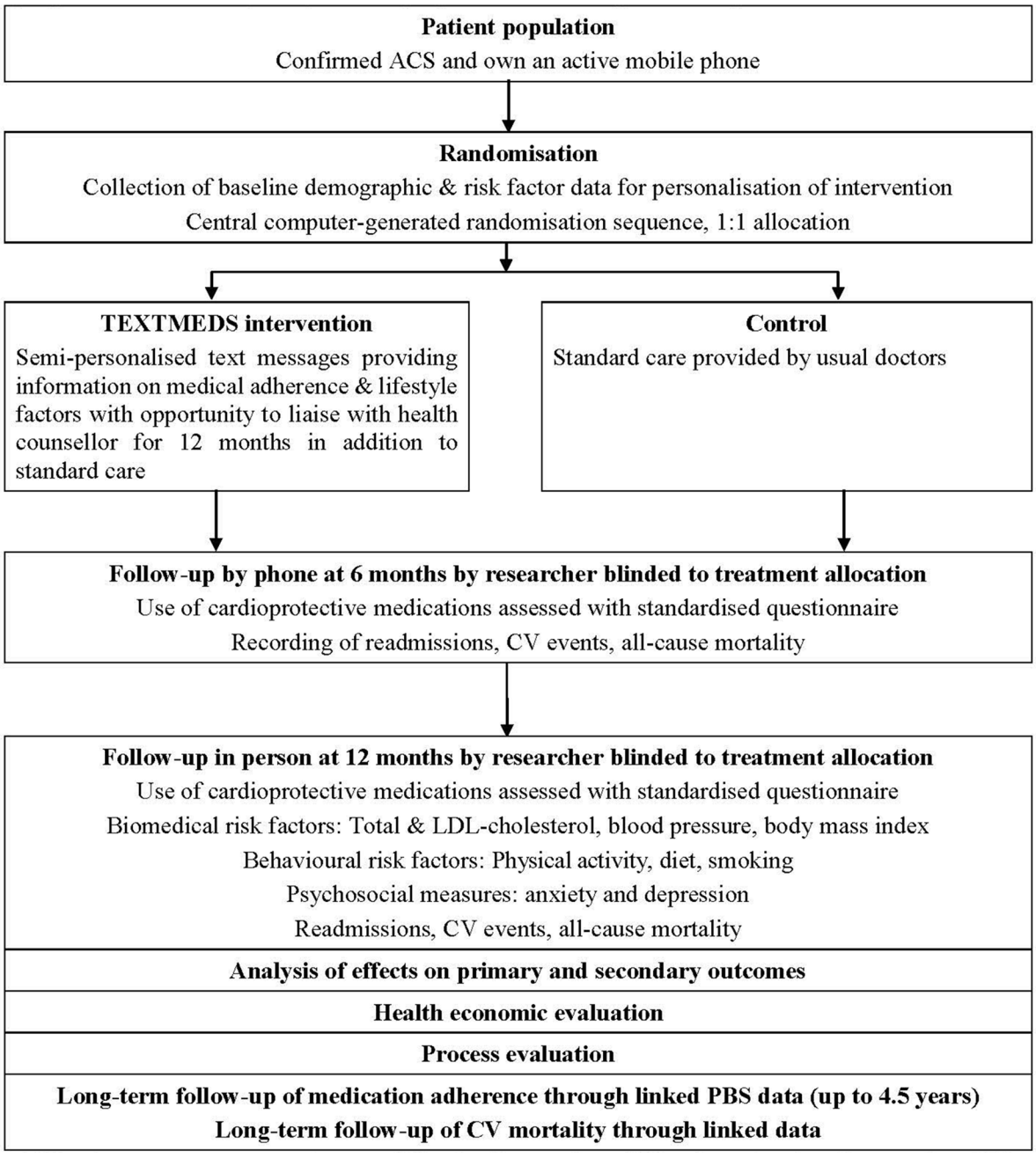

Figure 1 Flow chart of study design. Patients with acute coronary syndromes are considered for inclusion in the study and randomisation is single blind, with allocation determined by computerised programme and initiated by computerised programme after discharge from hospital. ACS, acute coronary syndrome; CV, cardiovascular; LDL, low-density lipoprotein; TEXTMEDS, TEXT messages to improve MEDication adherence and Secondary prevention.

Patients must also meet the following inclusion criteria: (1) ability to provide informed consent, (2) own an operational mobile telephone and (3) can read text messages in English on a mobile phone and (4) life expectancy more than 6 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 (CV) medications and referral to a centre-based cardiac rehabilitation or other secondary prevention programme.

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

Box Examples of text messages sent to the intervention group[27 31]

Introductory message

Hi <NAME>, Welcome to TEXT messages to improve MEDication adherence and Secondary prevention (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

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

BBQ, Barbeque; BP, blood pressure.

Message content, frequency, sequence

The text message intervention builds on 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 CV 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 programme 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 programme. Each participant receives a customised and personalised set of messages (box). 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 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, for example, 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 3 working days.[28] The health counsellor has health professional qualifications (eg, 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 subspecialty 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 programme 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 software administering the intervention to customise and personalise messages. The programme 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.

Data collection and study outcomes

The follow-up study assessments will occur at 6 months over 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 inhibitor or angiotensin II receptor blockers, (2) beta-blocker, (3) statin lipid-lowering, (4) aspirin and (5) 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 6-month 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 6-month and 12-month visits.[19] Indicated medications will be all five classes of guideline recommended medications listed above unless a contraindication 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 BP (raised BP). Other secondary outcomes include: total cholesterol, diastolic BP, the proportion of participants adherent to each medication class, other CV risk factors including behavioural risk factors, psychosocial factors, major CV events, hospital readmissions and all-cause mortality and composites of risk factor control and major adverse CV events (table 1). A formal endpoint adjudication process will be implemented and includes a review of original documents for major CV 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 randomisation 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 The George Institute (TGI) with data entry through a password protected, web-based interface by registered staff, real-time data query generation for values entered outside of preset 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 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[42]	✓		✓
Fruit and vegetable intake	WHO Steps instrument[43]	✓		✓
Anxiety symptoms	Generalised Anxiety Disorder 7-item scale[44]			✓
Depressive symptoms	Patient Health Questionnaire[45]			✓
Quality of life	SF-12_V2 Health Survey[35]	✓		✓
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.

Process measures

Process evaluations explore the implementation, receipt and setting of an intervention and assist in the interpretation of outcome results.[32] Analyses will be informed by the Pawson and Tilley realistic evaluation model,[33] 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 TEXT-MEDS strategy may or may not have been effective and which intervention components were most influential.

The process evaluation will include a semiquantitative 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 the utility and acceptability of the intervention programme. 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 programme. 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.[34] 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 12-item Short Form Survey Version 2 (SF-12_V2) Health Survey[35] (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 CV 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 CV events from literature review.[36] Long-term costs and QALYs will be modelled using a decision analytic Markov model that will enable us to extrapolate beyond the data collection period, predict within the cohort the occurrence of CV events over a lifetime and thus estimate longer-term costs, potential cost savings and benefits of the intervention.[37]

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.[38] To test for a 10% improvement in the primary outcome relative risk (RR of 1.10) in the treatment compared with the control arm (assuming ~70% of patients are taking appropriate secondary prevention in control arm, based on contemporary Australian registry data,[39 40] 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 (1) 0.15 mmol/L in LDL-cholesterol assuming a SD of 0.92 mmol/L,[41] (2) 2.7 mm Hg in systolic BP, assuming an SD of 17 mm Hg[41] and a minimum detectable RR of 0.69 in CV events assuming a major CV event rate of 19% or a power of approximately 13% to detect a RR of 0.80 in CV events, assuming a lower CV event rate of 5% at 12 months from contemporary Australian data.

The intention to treat principle will be used and patients will be analysed 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 χ^2 test. The primary analysis will be unadjusted. The mean level of BP and cholesterol will be analysed using an analysis of covariance using the baseline values as the 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 RRs for dichotomous variables along with the 95% CIs and two-sided P values.

We will also analyse 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 CV events will be compared between treatments using a χ^2 test. The criterion for statistical significance will be set at α=0.05. Number needed to treat 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 CVD 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 V.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 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 programme 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 programme 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 CV 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 BP, which are both strong and objective measures of CV risk. We will also be examining the impact of the intervention programme on behavioural risk factors, which our predecessor study to this, TEXT ME, demonstrated a substantial impact.

In our previous single-centre study—TEXT ME, our group has demonstrated that a lifestyle-focused text-messaging programme was associated with reductions in LDL-cholesterol, BP, body mass index 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 to 4.02).[17] The TEXTMEDS study will extend the knowledge from the TEXT ME study by examining the impact of a longer text message programme (12 months vs 6 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 programme delivered via text messages has the advantages of low cost and being easily automated. These elements can allow these programmes 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 multicentre randomised controlled data on whether a cardiac prevention programme 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

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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Contributors CKC had the original idea. JR, AT, DB, GSH, AR, SJ and DPC were involved in study design and protocol development. SS and LB contributed to the design of the statistical analysis approach. KS, CK, JT, RJ and KR, were involved in literature review and developing study instruments and materials. JJA, RB, NC, SC, CH-C, NK, AM, MMG, PS and PT are site PI involved in providing a critical review of the manuscript. All authors read and approved the final manuscript.

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