BMJ Open

Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028017
Article Type:	Protocol
Date Submitted by the Author:	20-Nov-2018
Complete List of Authors:	Bermon Angarita, Anderson; Fundacion Cardiovascular de Colombia, Research Uribe Rodríguez, Ana; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Pérez-Rivero, Paula; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Prieto-Merino, David; London School of Hygiene & Tropical Medicine Cáceres Rivera, Diana ; Universidad Cooperativa de Colombia, Nursing Guio, Elizabeth; Fundacion Cardiovascular de Colombia, Metabolism and Genoma Laboratory Atkins, Louise; University College London Research Department of Epidemiology and Public Health Horne, Robert; University College London Murray, Elizabeth; University College London, Primary Care and Population Health Serrano Díaz, Norma; Fundación Cardiovascular de Colombia, Direction of research Free, Caroline; London School of Hygiene and Tropical Medicine, Public Health interventions Unit Perel, Pablo; LSHTM, EPH Casas, Juan Pablo ; University College London Medical School, Clinical Epidemiology and Informatics ; Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Anderson Bermon Angarita[1]
Fundación Cardiovascular de Colombia
Research department
Av. 5 # 6-33, Floridablanca, Santander, Colombia.
Postal code: 681004
Telephone number: (+57) 3002053041
FAX: (+57) 6796470
andersonbermon@fcv.org

Ana Fernanda Uribe Rodríguez
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

Paula Fernanda Pérez-Rivero
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

David Prieto-Merino
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine
London, UK

Diana Isabel Cáceres Rivera
Cooperativa Colombia University
Faculty of Nursing
Bucaramanga, Santander, Colombia

Elizabeth Guio
Metabolism and Genome Laboratory
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Lou Atkins
Faculty of Health Psychology
University College London
London, UK.

Robert Horne
Centre for Behavioural Medicine
UCL School of Pharmacy
University College London
London, UK.

Elizabeth Murray
Research Department of Primary Care and Population Health

[1] Corresponding author

University College London
London, UK.

Norma Cecilia Serrano Díaz
Research Department
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Caroline Free
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Pablo A. Perel
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Juan P. Casas
Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
VA Boston Healthcare System
Boston, Massachusetts, USA.

Keywords: Cardiovascular diseases, Health behavior, Medications adherence, mHealth, text messaging

Word count: 5309

Abstract

Introduction: Evidence has shown that in patients with Atherosclerotic cardiovascular diseases (ASCVD) anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins, are cost-effective in reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that adherence to these cardiovascular medications is far from ideal. A recent Cochrane review showed a beneficial effect of SMS interventions on adherence to medication in ASCVD patients.

Methods and analysis: Txt2heart study is a pragmatic randomized single blind controlled trial. The objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobiles phones to improve adherence to cardiovascular medications in patients with ASCVD. The intervention consists on behavioural techniques delivered thorough SMS. The primary outcomes are: Blood serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as an indicator of adherence to blood-lowering therapies and heart rate as an indicator of adherence to beta blockers. Secondary outcomes will include: Urine levels of 11 dhTxB2, adherence to cardiovascular medications and rates of cardiovascular death or hospitalization due to cardiovascular disease.

Ethics and dissemination: The study will be conducted in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial. Txt2 heart Colombia trial is aimed to provide high level evidence that

evaluate whether SMS messages delivered through mobile telephony, change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the health local authorities and if the intervention turns out to be effective and safe, we hope this strategy would be implemented soon considering its low cost and wide-reach to the population.

Trial registration number: ClinicalTrials.gov: NCT03098186

Strengths and limitations of this study.

This trial uses biomarkers to evaluate medication adherence.

This trial uses an innovative intervention through SMS methodology based on behavior theories

There is, however a variability in time of biomarkers, therefore we will use two additional measures to evaluate adherence.

Tabla 1.

Summary

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT03098186
Date of registration in primary registry	March 10, 2017
Source(s) of monetary or material support	Departamento Administrativo de Ciencia, Tecnología e Innovación Colombia COLCIENCIAS Fundación Cardiovascular de Colombia London School of Hygiene and Tropical Medicine University College, London Universidad Pontificia Bolivariana

Primary sponsor	COLCIENCIAS Contact: contacto@colciencias.gov.co (+57) (1) 6258480 ext. 2081
Secondary sponsor (s)	Fundación Cardiovascular de Colombia
Contact for public queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Contact for scientific queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Public title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol
Scientific title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol
Countries of recruitment	Colombia
Health condition(s) or problem(s) studied	Acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation) Stable angina Ischemic cerebrovascular disease Peripheral arterial disease
Interventions	Active treatment: will consist of SMS that are aimed to modified behavioural factors associated with poor adherence to cardiovascular medications used in secondary prevention. The SMS will be delivered daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th. In addition, they will receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly. Control: participants will only receive SMS thanking for their participation in the trial, reminders of trial appointment and

	informing if they have changed contact details. The frequency of this SMS will be monthly.
Key inclusion and exclusion criteria	Inclusion Criteria: Age ≥18 years old Sexes eligible for study: both History of at least one of the following arterial occlusive events: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Own at least one mobile phone Ability to read and understand text messages (SMS) Intention to stay in the country of recruitment during the next 12 months Exclusion Criteria: Contraindication to take all cardiovascular medications used in secondary prevention. Participation in another randomized clinical trial that could interfere with adherence to treatment.
Study type	Two-parallel arm, only-blind, individually randomized controlled trial.
Date of first enrolment	April 2017
Target sample size	1600
Recruitment status	Recruiting
Primary outcome(s)	Differences in changes (baseline minus 12 months) of: Low density lipoprotein cholesterol (LDL-C) Systolic Blood pressure Heart Rate

Key secondary outcomes	Differences in the changes (baseline minus 12-months) of: (i) Adherence to cardiovascular medications used in secondary prevention measured by MARS-5 questionnaire; and (ii) Urinary levels of 11 dh-TxB2. Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months. Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months Adverse events: traffic accidents and injuries while reading SMS related to the trial.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death worldwide. Every year, around 35 million people worldwide have an acute coronary event or cerebrovascular event, and one quarter of these events occur in people with established ASCVD[1]. In low & middle-income countries (LMICs) these arterial occlusive events occur at an early age, affecting economically active populations resulting in large economic impacts[2].

Evidence from randomised controlled trials (RCTs) has shown that in patients with established ASCVD anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins, are cost-effective in reducing the risk of ASCVD events and are included in the list of the World Health Organization (WHO) Essential Medicines List (EML)[3]. It has been estimated that treatment with these four proven medications (together with smoking cessation) will prevent or postpone around 75-80% of recurrent vascular events and their complications, such as death and disability[4].

Unfortunately, there is abundant evidence that world-wide adherence to these cardiovascular medications in patients with ASCVD is far from ideal. In high-income countries, less than half of patients with known ASCVD disease are receiving the all group of cardiovascular medications, with the situation being much worse in LMICs. The PURE study showed that in LMICs only 1 in 20 patients with ASCVD are receiving the four types of cardiovascular drugs[5].

A wide range of socio-economic and service level factors influence whether patients obtain medications including the availability of medication (drug stock outs), lack of

affordable medication and service factors such as the availability and training of health care providers. Adherence to medication focuses on whether patient take medication that is prescribed. Two recent systematic reviews on patient factors that affect adherence to ASCVD medications in secondary prevention showed that these go far beyond simply "forgetting" to take medication and include a range of factors including patients' perceptions of the cause and prognosis of the illness(e.g. fatalistic perceptions or absence of symptoms) and / or the risks and benefits of medications (e.g. fear of side-effects or concern about multiple medications); patient-physician relationship; availability of family/social network support; and comorbidities (e.g. depression) amongst others[6 7].
A recent systematic review from RCTs on interventions to improve adherence to medications in patients with ASCVD has shown that there are several potential interventions, and, importantly, that simple interventions might be as effective as complex ones (and therefore easier to replicate)[8]. However, this review also highlighted many limitations in the current evidence such as risk of bias, small sample sizes and lack of studies in LMICs where most of the patients with ASCVD live. Among the most promising simple strategies to increase adherence this review singled out Short Message Services (SMS) interventions.

Mobile phones have become an "essential" instrument of daily-life worldwide, with around ~7 billion subscribers of whom 78% are based in LMICs[9]. This makes mobile phones an "ideal instrument" to deliver health behaviour change interventions to large numbers of people at low cost. Systematic reviews of RCTs using mHealth interventions confirm that SMS can be successful in changing behaviour, including smoking cessation and improved adherence to HIV medications[10,11]. Patient factors influencing adherence, such as knowledge attitudes and beliefs could be amenable to change using mobile phone messages sent to patients.
A recent Cochrane review evaluated the effects on adherence to medications of SMS in patients with ASCVD[12]. The review identified seven trials (1310 participants) and showed a beneficial effect of SMS on adherence to medication in six of them. However, the quality of the evidence was very low. Limitations identified by the Cochrane review were: (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV) the majority of studies recruited only patients with acute coronary syndrome leaving out an important group of patients with other arterial occlusive events (e.g. ischemic stroke, peripheral vascular disease and programmed coronary revascularizations) that should be amenable for such type of intervention; (V) few studies were conducted in LMICs; and (VI) most trials did not describe the processes behind the SMS content generation, and

few that reported them did not target the key knowledge and attitudinal factors known to influence adherence to medication; instead interventions were simple “reminders”.

In conclusion, given the high prevalence of people with ASCVD in LMICs and the low use of cost-effective secondary prevention medications, a low-cost intervention that builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to improve public health. The current evidence shows that SMS interventions based on change behavior techniques are a potentially effective strategy to increase adherence to medications in people with ASCVD, but further large trials are needed.

To provide the high-quality evidence needed to assess the effect of SMS interventions based on change behavior techniques to increase adherence to medications in patients with ASCVD we have designed the txt2heart study, which is a large pragmatic superiority parallel randomized single blind controlled trial with a 1:1 allocation ratio that will evaluate the efficacy and safety of SMS on adherence to cardiovascular medications. The trial is being conducted in a setting (Colombia) where patient factors such as knowledge attitudes and beliefs are important determinants of adherence. In this context medicines are widely available and generally affordable, so an intervention delivered to patients via SMS has the potential to be effective.

METHODS AND ANALYSIS

This protocol is reported following the SPIRIT Standard Protocol Items recommendations for Interventional Trials[13].

Aim and objectives

The primary objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobiles phones to improve adherence to cardiovascular medications in patients with atherosclerotic cardiovascular disease (ASCVD).

Secondary objective is to assess the impact of the mobile text messaging on adherence to medications, hospitalizations, and the composite end-point of incident Major Adverse Cardiovascular Events (MACE) at 12 months.

Choice of comparator

The trial design is a two-parallel arm in which the comparator is a placebo follow up. Patients allocated to placebo group will receive messages with gratefulness and update content. In the choosing of comparator we evaluated the possible harm or discomfort to participants and we considered there not will be any harm from receiving this kind or messages. We will explain participants they could be allocated in one of two different groups and what the differences are in each one. Furthermore, our intervention will not interfere with medical treatment, patients will be warned that the study does not pretend to replace medical assistance and that they must continue with their traditional treatment.

Trial design

Txt2 Heart Colombia is a two-parallel arm, only-blind individually randomized controlled trial. This design is aimed to minimize any potential bias that affects the internal validity of the study. The selection criteria have been designed to increase the number of potential beneficiaries of the intervention and to keep the selection process as close as possible to the future scenario in which the intervention will be implemented. Therefore, Txt2THeart-Colombia is pragmatic in design. The active intervention will be the SMS delivered by mobile phones and the content of the SMS is aimed to modified behaviour associated with poor adherence to ASCVDs medications in ASCVDs patients. Randomization will be performed as block randomization with a 1:1 allocation.

Study setting

We will recruit patients at Fundación Cardiovascular in Colombia which has a staff knowledgeable in trials and enough pool of eligible patients.). The trial will continue to add sites if necessary, to ensure the sample size is achieved. There is no limit to the maximum number of patients to be recruited in each site.

Eligibility criteria

Inclusion criteria: Adult patients ≥ 18 years old with a history of at least one of the following arterial occlusive events: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Patients should own a mobile phone and be able to read SMS.

Exclusion Criteria: Known contraindication to take all appropriate cardiovascular secondary prevention medications.

Intervention

The intervention being evaluated *behavioural change techniques* (BCT) delivered through SMS. We have developed our intervention following the recommendations by Abroms et al[14]. First, we reviewed the literature on individual level factors influencing adherence to medication[6]. Subsequently, we conducted country-specific qualitative studies focus group discussions and semi-structured interviews to evaluate cardiovascular patient's perceptions about mHealth programmes and to determine which variables we need to address in our intervention. To construct the content of the SMS, we wrote messages employing educational and enabling behaviour change functions and 6 established BCT to target the potentially modifiable factors influencing adherence referred in the literature and found in our qualitative studies[15]. Finally, we tested the SMS messages with participants and adapted the messages based on their feedback to ensure the messages were understandable, acceptable, and relevant. The resultant intervention delivered by SMS provides information about health consequences of adherence or non-adherence, instruction on how to take medication, medicine taking prompts and cues, support in getting into medicine taking habits, reframes medicine taking and provides or encourages social support for taking medication. The messages were designed according to the Transtheoretical Model (Prochaska & DiClemente, 1992) and were aimed to enhance actions related with the steps and processes of this model. We will send messages daily the first month, the second month three times per week and the last ten months once per week. The intervention will be delivered through and electronical platform and it will be one-way intervention. Due to lack of economic resources we will not tailor the messages. The trial intervention starts the day after recruitment and continues for 12 months or until the participant withdraws from the study or dies. The follow-up duration will be at least of 12 months and maximum of 36 months. Participants will not receive messages after month 12.

Outcomes

The primary outcomes have been selected for their clinical relevance and are differences in changes (12 months "minus" baseline) in: *Blood serum LDL-C levels* as an indicator of adherence to statins, *systolic blood pressure* as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and *heart rate* as an indicator of adherence to beta blockers.

Secondary outcomes will include: *Urine levels of 11 dhTxB2* as an indicator of adherence to antiplatelet therapy, *adherence to cardiovascular medications* used in secondary prevention measured by MARS-5 questionnaire. Rates of cardiovascular death or hospitalization due to cardiovascular disease and non-cardiovascular death or

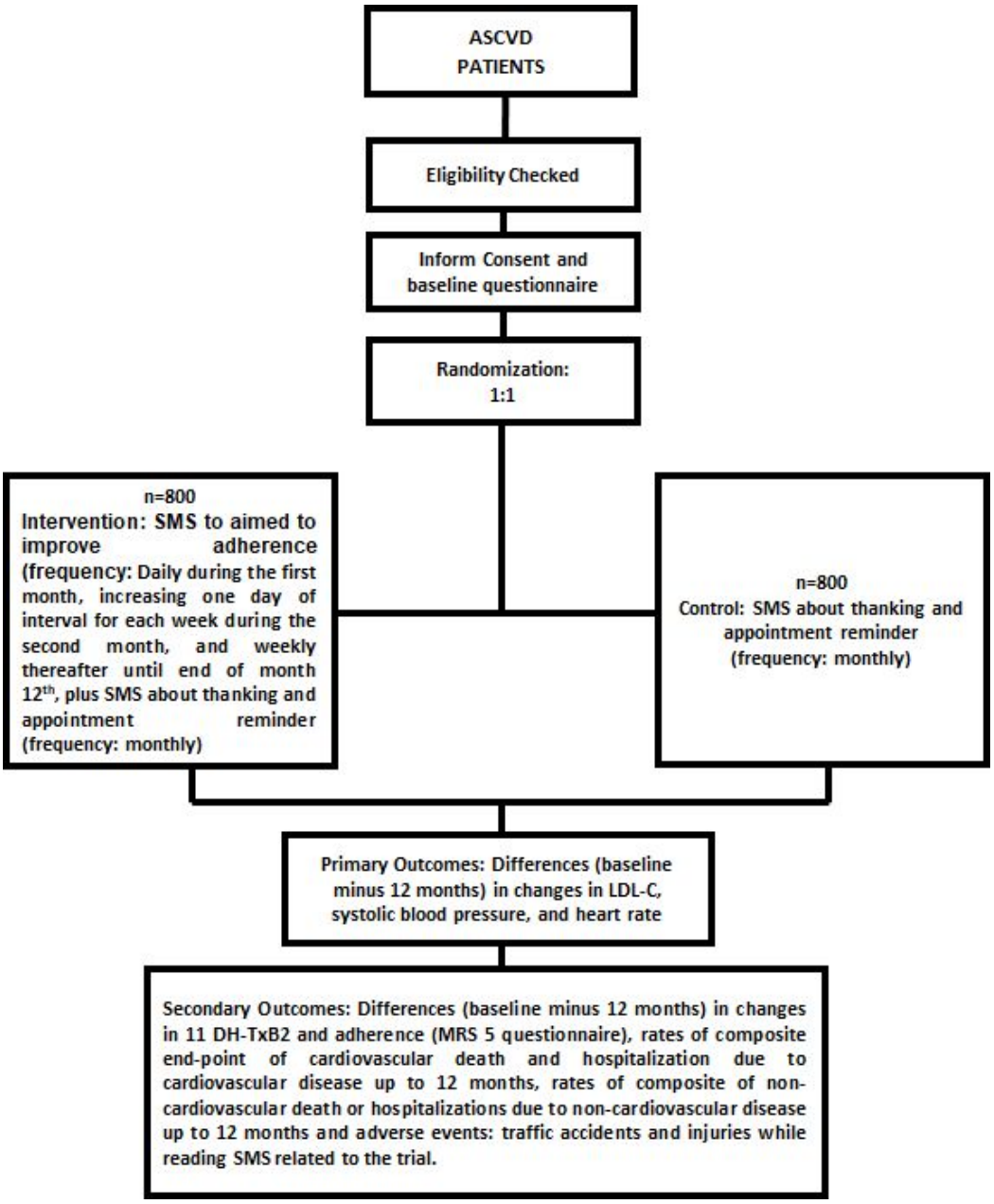
hospitalizations due to non-cardiovascular disease. We will also include road traffic crashes (the only potential known hazard of text messaging) and death due to all causes as secondary outcomes.

Participant timeline

Participants who fulfil the eligibility criteria and provide their informed consent, will be recruited into the txt2heart trial. At first visit, after the participant has provided informed consent, baseline characteristics will be collected through questionnaires (MARS-5 and PHQ-9 Patient Health Questionnaire), blood samples, blood pressure, and heart rate. Participants will be then randomised to the intervention or control arm. The trial intervention will start the day after recruitment and will continue for 12 months to a maximum of 36 months, or when the participant withdraws from the study, or dies. Three months later, during the second visit, we will conduct a phone follow up interview to evaluate adequate SMS delivery and occurrence of clinical events. Finally, in the third visit (12 months later) we will collect data on adherence to cardiovascular medications (MARS-5), blood pressure, heart rate and clinical end-points. The 12 months follow up marks the primary outcome point. For patients with follow up beyond 12 months, we will have (by phone) assessment of clinical outcomes (death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization) every 6 months until 36 months, the longest available follow-up.

Figure 1.

Trial flowchart



*Elaborated by the authors

Sample Size

The sample size of the study is 1600 participants, the power of the study was calculated for differences between arms in the reduction of the primary outcome LDL-C (12-month minus baseline).

The power of the study was calculated for the primary outcomes of the clinical trial: differences in the levels of physiological markers of adherence to cardiovascular drugs. Because in this study the power of a sample size depends on several parameters such as what doses are finally prescribed to patients and what proportion of patients will adhere, we did several power and sample size calculations for different scenarios. We concluded that 1600 is a reasonable sample size. For example, assuming that adherent patients to Atorvastatin 40mg for 12 months are expected to have an average LDL-cholesterol reduction of 91.3 mg/dL (data derived from randomized clinical trials), while non-adherent patients will reduce LDL-cholesterol by an average of 18.3 mg/dL (or 20% of the reduction in adherent patients), and that the standard deviation of the changes is around 27.07 ml/dL, we would have 97% power to detect a 7% difference in adherence between arms or a 77% power to detect a 5% difference (always using a 5% type-I error). If, however, patients were on Atorvastatin 20 and the expected reductions of LDL-C were 80.05 mg/dL in adherent and 16.01 mg/dL in non-adherent patients, then we would have a 91% power to detect a 7% difference of adherence between arms and a 66% power to detect a 5% difference between arms.

Table 2:

Sample size calculations

Statins and its frequency in trials		Reduction of LDL after a year of treatment in adherents and non-adherents			Power to detect differences depending on adherence increase		
	%	**AD=yes**	**AD=No**	**Dif**	**5.0%**	**7.0%**	**10.0%**
Atorvastatin 10	1.5%	1.79	0.36	1.43	53%	82%	98%
Atorvastatin 20	32.9%	2.07	0.41	1.66	66%	91%	100%
Atorvastatin 40	52.4%	2.36	0.47	1.89	77%	97%	100%
Atorvastatin 80	9.4%	2.64	0.53	2.11	85%	99%	100%
Fluvastatin 20mg	0.0%	1.02	0.20	0.82	21%	37%	64%
Lovastatin 40	0.0%	1.77	0.35	1.42	53%	81%	98%
Pravastatin 10	0.0%	0.95	0.19	0.76	19%	33%	58%
Pravastatin 20	0.0%	1.17	0.23	0.94	27%	46%	76%
Pravastatin 40	0.0%	1.38	0.28	1.10	35%	60%	88%
Rosuvastatin 5	0.0%	1.84	0.37	1.47	56%	84%	99%
Rosuvastatin 10	0.3%	2.08	0.42	1.66	66%	91%	100%
Rosuvastatin 20	1.7%	2.32	0.46	1.86	76%	96%	100%
Rosuvastatin 40	1.6%	2.56	0.51	2.05	83%	98%	100%

Simvastatin 10	0.0%	1.31	0.26	1.05	32%	55%	85%
Simvastatin 20	0.1%	1.54	0.31	1.23	42%	69%	94%
Simvastatin 40	0.2%	1.78	0.36	1.42	53%	81%	98%
Simvastatin 80	0.0%	2.01	0.40	1.61	63%	90%	100%

*Elaborated by the authors

Power is calculated assuming a sample size of 800 per arm, 5% type-I error, a standard deviation of of the LDL change of 0.7, and that non-adherent patients will still reduce their LDL on average 20% of the reduction of adherent patients

Interpretation of the table: Example of third line (Atorvastatin 40): 52.4% of patients in the hospital take Atorvastatin 40. Adherent patients are expected to reduce their cholesterol an average of 2.36 mmol/l in the first year while non-adherent patients are expected to reduce it 0.47 mmol/l. If all patients were on Atorvastatin 40 we would have a 77% power to detect a true increase of adherence of 5%, a 97% power to detect a true increase of adherence of 7% and almost a 100% power to detect a true increase in adherence of 10%. Atorvastatin is the most prescribed statin among patients in our study. About the 65% of the sample use.

Recruitment

The pragmatic nature of this trial will allow collaborators to follow different strategies for participant recruitment according to the setting. There are three main approaches for recruitment of patients who fulfil the inclusion criteria a) in hospital patients at the time of discharge, b) patients attending outpatient clinics, c) and patients who are in the health care facility database and who will be contacted by phone calls and will be recruited in outpatient clinics.

Assignment of intervention

Randomisation: We will use block randomisation (varying size), stratifying by centre and with 1:1 allocation between the intervention and control arm. Randomisation will be conducted centrally through the CommCare platform after eligibility criteria has been confirmed, informed consent signed, and baseline information collected. The randomised allocation will therefore not be revealed until after a participant has formally been entered onto the trial; hence concealment of allocation will be complete. The SMS will be automatically generated by the CommCare platform, unknown to investigators in contact with patients.

Blinding: Because of the nature of the intervention (SMS messages) it is not possible to blind participants. However, the tx2theart trial will conduct a blinded assessment of

outcomes. Research personnel collecting data on clinical events, adherence scales, and biomarkers will not have access to treatment allocation. The laboratory results will be conducted once trial follow-up is completed. Are there going to be SOPS (Standard Operating Procedures) for measuring BP, heart rate? And are the bloods all going to be analysed in the same lab? Or different ones? Even if the same one, are there standardized procedures, and will there be some way of checking that changes over time are not simply due to measurement error?

Data collection methods

Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered in the CommCare platform, designed by Dimagi. CommCare is an open source mobile platform designed for data collection, client management, decision support, and behaviour change communication. The electronic devices (desktop computers, laptops and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by Fundación Cardiovascular de Colombia. Methods used to ensure high follow up achieved?

Clinical outcomes

Death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization will be defined by local investigators based on clinical notes, and clear objective criteria using the suggestions provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials[17].

Self-reported adherence

To estimate adherence, we will use a self-reported scale named Medication Adherence Report Scale 5 (MARS-5) which has shown to be a valid and reliable scale for measuring adherence to medication in chronic conditions at the trial entry and at the final assessment at 12 months[18]. The MARS-5 Scale elicits patients' reports of non-adherence. To diminish the social pressure on patients to report high adherence, items are phrased in a non-threatening manner and patients are assured that their responses will be anonymous and confidential. Participants are asked to rate the frequency with which they engaged in each of five aspects of non-adherent behaviour listed (e.g. 'I forget to take these medicines', 'I stop taking these medicines for a while') using a 5-point scale ranging from 'never' to 'always'. Scores for each item are summed to give a total score ranging from 5 to 25, with higher scores indicating higher levels of adherence

Biomarkers

Physiologic measurements heart rate and blood pressure will be measured with a calibrated Omron® device (Ref: HEM-7114) using Standard Operating Procedure by trained health care professionals. Patients are going to sit quietly for 10 minutes before the examinations.

Blood LDL-C: Quantification of serum LDL will be performed using automated equipment by direct method.

Recent large epidemiological studies have confirmed that resting heart rate is an independent predictor of cardiovascular mortality. Heart rate decreasing is itself an important mechanism of benefit of the blockers and other drugs that reduce heart rate after an acute myocardial infarction(1–4). There are still controversies regarding the optimal dosage to obtain results, but the reduction in heart rate is notorious in patients receiving beta blockers (5). In Colombia, betablockers are a first-line drug used for secondary prevention, the most frequently is carvedilol, which has evidence of advantages in decreasing heart rate and decreasing mortality in patients with some type of cardiovascular event (6).

Data management

Data will be held on a secure system and will be password protected. All trial procedures will be in accordance with the principles of Good Clinical Practice (GCP). Essential documents of the sponsor/trial organizers and investigators will be retained for 15 years least ten years after completion of the trial. The research staff will maintain appropriate medical and research records for this clinical study, meeting the regulatory and institutional frameworks for the protection of the confidentiality requirements. As sponsor of this trial, Fundación Cardiovascular de Colombia will allow that regulatory agencies could examine (under applicable law) clinical records to check the quality, safety and progress of the study.

Statistical Analysis

The main analyses will be an “intention to treat”, meaning it will compare all those allocated to the intervention versus those allocated to the control arm, irrespective of whether they received the allocated intervention or not. A sensitivity per protocol analysis will also be conducted. For continuous outcomes (including all primary outcomes: LDL cholesterol, blood pressure and Heart rate), we will estimate an ANCOVA model regressing the 12-month difference from baseline on the allocated group and the mean centred baseline values of the continuous variable. Deaths and hospitalizations will be analyzed with a cox regression models estimating hazard ratios. The assumptions

underlying all these models will be assessed. For subgroup analyses we will only consider a limited number of variables that, given the mechanism of action of the intervention, could modify the effect of the intervention. A detailed statistical analysis plan setting out full details of the proposed analyses will be prepared and completed before the trial database is locked for final analysis. Missing data will be managed by intention to treat analysis.

Data Monitoring

Data monitoring will be executed according with the GCP Guidelines. This trial is a large, pragmatic, randomised controlled trial. The intervention is a strategy (SMS) to change behaviour and increase adherence of safe and proven effective interventions for secondary prevention that have been in clinical use for decades. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring because of participation in this research study has been assessed as low risk to participants in each of these categories. Based on the low risks associated with this trial, there will not be a Data Monitoring Committee, however a Monitoring Plan to assure appropriate conduct of the trial will be developed which will incorporate 100% central monitoring in conjunction with procedures such as investigator training and meetings and written guidance. In addition, all data will be subject to statistical monitoring and at least 10% of data will be subjected to on-site monitoring. Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial related, and source documents must be kept for 15 years after the end of the trial.

Indirect Patient and Public Involvement

We did not directly include PPI in this study. However, to design the intervention, we interviewed patients regarding they perceptions about e-health and their previous experience with mobile cellphones technology. Additionally, The Ethics Committee that evaluated and approved our research included patients' representatives.

ETHICS AND DISSEMINATION

Protocol amends

Protocol trial has not been modified.

Ethical considerations

The study will be conducted in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki.

Ethical approval

The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial.

Informed Consent:

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient will be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. The written consent must be given by the patient and/or the legal guardian of the patient, after detailed information about the study has been given as in accordance with any national provisions on the protection of clinical study patients. The verbal explanation will cover all the elements specified in the written information provided for the patient. Patients and/or legal guardians will be required to sign and date the informed consent form. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study. The trial will include a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or law of protection of personal data, where the study team is authorized to handle personal and clinical data of the subject. Calls made in the pre-selection and visit phase 2 must be recorded and stored for a set time. Eligible participants can only be included in the study after sign “Txt2Heart-Colombia” informed consent (testified, where required by law or regulation), approved by the ethics committees. The process must be documented in the patient source documents specifically in CRFs (Case Report Form).

Confidentiality: Information about the study subjects will be kept confidential. The investigators will ensure the anonymity of patients; patients will not be identified by name in any document. Informed consent forms and patient recruitment registration will be kept strictly confidential only to permit identification of the patient at Fundación Cardiovascular de Colombia. Information about the study subjects will be handled under the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law of data protection). Those regulations require an authorization signed by the patient including the follow information: What protected health information (PHI) will be collected from the study subjects, who will have access to that information and why, who will use and disclose that information and the right to withdraw his/her authorization to use their PHI.

Access to data

Principal investigator and sub investigators will have access to the data in order to verify and analyses the results. To ensure confidentiality all the investigators will be blinded of participants identification.

Ancillary and post-trial care

Due to its low risk intervention this trial will not include an insurance for participants. However, we will refer patients to their medical services in the cases we consider they need assistance. Furthermore, a full explanation of the scope and limitations of the study will be told to the patients before they sign the informed consent.

Dissemination policy

Txt2 heart Colombia trial is aimed to provide high level evidence that evaluate whether SMS messages delivered through mobile telephony, change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the health local authorities and if the intervention turns out to be effective and safe, we hope this strategy would be implemented soon considering is low cost and wide-reach to the population.

Results from the trial will be published in an open journal in order scientist, clinicians and policymakers could access to de data.

REFERENCES

1. Perel, P., et al., *Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease.* Glob Heart, 2015. **10**(2): p. 99-110.
2. Perel, P., et al., *Noncommunicable diseases and injuries in Latin America and the Caribbean: time for action.* PLoS Med, 2006. **3**(9): p. e344.
3. World Health Organization. *Model List of Essential Medicines (20th List)*. 2017 [cited [Accessed June 23 2017]; Available from: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.
4. Yusuf, S., *Two decades of progress in preventing vascular disease.* Lancet, 2002. **360**(9326): p. 2-3.

5. Yusuf, S., et al., *Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey.* Lancet, 2011. **378**(9798): p. 1231-43.
6. Rashid, M.A., et al., *Medication taking in coronary artery disease: a systematic review and qualitative synthesis.* Ann Fam Med, 2014. **12**(3): p. 224-32.
7. R.M., *Patient factors that influence cardiovascular medication adherence (MSc Thesis)*. 2014, London School of Hygiene & Tropical Medicine.
8. Santo, K., et al., *Interventions to improve medication adherence in coronary disease patients: A systematic review and meta-analysis of randomised controlled trials.* Eur J Prev Cardiol, 2016. **23**(10): p. 1065-76.
9. International Telecommunications Union. *ICT Facts and figures*. 2014 [cited [Accessed July 20, 2017]; Available from: http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2014-e.pdf.
10. Free, C., et al., *The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review.* PLoS Med, 2013. **10**(1): p. e1001362.
11. Catalani, C., et al., *mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature.* Open AIDS J, 2013. **7**: p. 17-41.
12. Adler, A.J., et al., *Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2017. **4**: p. Cd011851.
13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Abroms, L.C., et al., *Developing and Pretesting a Text Messaging Program for Health Behavior Change: Recommended Steps.* JMIR Mhealth Uhealth, 2015. **3**(4): p. e107.
15. Michie, S., et al., *The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions.* Ann Behav Med, 2013. **46**(1): p. 81-95.
16. Moore, G.F., et al., *Process evaluation of complex interventions: Medical Research Council guidance.* BMJ, 2015. **350**: p. h1258.
17. Hicks, K.A., et al., *2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards).* Circulation, 2015. **132**(4): p. 302-61.
18. Mahler, C., et al., *Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany.* J Eval Clin Pract, 2010. **16**(3): p. 574-9.
19. Guerriero, C., et al., *The cost-effectiveness of smoking cessation support delivered by mobile phone text messaging: Txt2stop.* Eur J Health Econ, 2013. **14**(5): p. 789-97.

Authors' contributions

Study director

Norma Cecilia Serrano Díaz, MSc: Senior researcher and Research Department Director at Fundación Cardiovascular de Colombia. Dr Serrano participated in the choosing of the biomarkers and the processing design of biological samples.

Principal investigator

Anderson Bermon Angarita, MSc: Junior researcher and epidemiologist at Fundación Cardiovascular de Colombia. Dr Bermon participated in the trial design and studied the impact of the results in Colombia, considering the healthcare system limitations.

Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor Faculty of Psychology, Pontificia Bolivariana University. Dr Uribe designed the messages intervention and studied the behavioural theories that support the intervention methodology.

Study chair

Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University College London at Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr Casas conceived the idea of conducting the trial and participated in methodology design of the trial

Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr Perel conceived the idea of conducting and participated in methodology design of the trial

Sub investigators:

Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research Department of Primary Care and Population Health, University College London. Dr Murray contributed in the intervention design and messages validity process.

David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr Prieto-Merino designed the statistical analysis and data management of the trial.

Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr Free conceived the idea of conducting and participated in the validity process of the messages intervention.

Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr Atkins contributed in the messages intervention design.

Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of Pharmacy, University College London. Dr Horne participated in the validity process of the messages intervention and the choosing of adherence scales.

Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación Cardiovascular de Colombia. Dr Guio participated in the choosing of the biomarkers and the processing design of biological samples.

Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at Cooperativa Colombia University. Dr Cáceres contributed in the trial design.

Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant researcher at Pontificia Bolivariana University. As young researcher Psy. Pérez participated in the intervention design.

Acknowledgements statement

We would like to thank to cardiology department medical staff at Fundación Cardiovascular de Colombia for their help with developing our research questions.

Funding statement

This work was supported by COLCIENCIAS code 656672553352 grant 899-2015

Fundación Cardiovascular de Colombia, Floridablanca
London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded Reference MR/N021304/1
Universidad Pontificia Bolivariana, Bucaramanga sectional

Competing interests statement

All authors declare there is not conflict of interest.

All funding institutions declare there is not conflict of interest.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#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	18
Roles and responsibilities: committees	#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)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies	5

		(published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	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, non-inferiority, exploratory)	7
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	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)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	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)	9
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	11

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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	12
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	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	13

		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	
Data collection plan: retention	#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	13
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	14
Statistics: outcomes	#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	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#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)	14
Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15

formal committee		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	
Data monitoring: interim analysis	#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	15
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
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)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
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	16
Dissemination policy: trial results	#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	17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	17

reproducible research		participant-level dataset, and statistical code	
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16
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	13

BMJ Open

Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028017.R1
Article Type:	Protocol
Date Submitted by the Author:	06-May-2019
Complete List of Authors:	Bermon Angarita, Anderson; Fundacion Cardiovascular de Colombia, Research Uribe Rodríguez, Ana; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Pérez-Rivero, Paula; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Prieto-Merino, David; London School of Hygiene & Tropical Medicine Cáceres Rivera, Diana ; Universidad Cooperativa de Colombia, Nursing Guio, Elizabeth; Fundacion Cardiovascular de Colombia, Metabolism and Genoma Laboratory Atkins, Louise; University College London Research Department of Epidemiology and Public Health Horne, Robert; University College London Murray, Elizabeth; University College London, Primary Care and Population Health Serrano Díaz, Norma; Fundación Cardiovascular de Colombia, Direction of research Free, Caroline; London School of Hygiene and Tropical Medicine, Public Health interventions Unit Perel, Pablo; LSHTM, EPH Casas, Juan Pablo ; University College London Medical School, Clinical Epidemiology and Informatics ; Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Research
Primary Subject Heading:	Public health
Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: The Txt2heart-Colombia randomized controlled trial protocol

Anderson Bermon Angarita*
Fundación Cardiovascular de Colombia
Research department
Av. 5 # 6-33, Floridablanca, Santander, Colombia.
Postal code: 681004
Telephone number: (+57) 3002053041
FAX: (+57) 6796470
andersonbermon@fcv.org
*Corresponding author

Ana Fernanda Uribe Rodríguez
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

Paula Fernanda Pérez-Rivero
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

David Prieto-Merino
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine
London, UK

Diana Isabel Cáceres Rivera
Cooperativa Colombia University
Faculty of Nursing
Bucaramanga, Santander, Colombia

Elizabeth Guio
Metabolism and Genome Laboratory
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Lou Atkins
Faculty of Health Psychology
University College London
London, UK.

Robert Horne
Centre for Behavioural Medicine
UCL School of Pharmacy
University College London
London, UK.

Elizabeth Murray
Research Department of Primary Care and Population Health
University College London

London, UK.

Norma Cecilia Serrano Díaz
Research Department
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Caroline Free
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Pablo A. Perel
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Juan P. Casas
Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
VA Boston Healthcare System
Boston, Massachusetts, USA.

Keywords: Cardiovascular diseases, Health behavior, Medications adherence, mHealth, text messaging

Word count: 5006

Abstract

Introduction: Evidence demonstrated that anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that adherence to these cardiovascular medications is far from ideal. A recent Cochrane review showed a beneficial effect of SMS interventions on adherence to medication in ASCVD patients.

Methods and analysis: The Txt2heart study is a pragmatic randomized single-blind controlled trial. The objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobile phones to improve adherence to cardiovascular medications in patients with ASCVD. The intervention consists of behavioural techniques delivered via SMS. The primary outcomes are blood serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as an indicator of adherence to blood-lowering therapies and heart rate as an indicator of adherence to beta-blockers. Secondary outcomes will include urine levels of 11 dhTxB2, adherence to cardiovascular medications and rates of cardiovascular death or hospitalization due to cardiovascular disease. More information is available in the supplementary files, trial summary (table 1.)

Ethics and dissemination: The study will be performed in compliance with the protocol, regulatory requirements, GCP and ethical principles of the Declaration of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to

evaluate whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the local health authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

Trial registration number: ClinicalTrials.gov: NCT03098186

Strengths and limitations of this study.

This trial uses biomarkers to evaluate medication adherence.

This trial uses an innovative intervention through SMS methodology based on behaviour theories.

However, there is variability in the time of biomarkers. Therefore, we will use two additional measures to evaluate adherence.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death worldwide. Approximately 35 million people worldwide have an acute coronary event or cerebrovascular event annually, and one quarter of these events occur in people with established ASCVD[1]. These arterial occlusive events occur at an early age in low and middle-income countries (LMICs), which affects economically active populations and resulting in large economic impacts[2].

Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the risk of ASCVD events in patients with established ASCVD, and these agents are included in the list of the World Health Organization (WHO) Essential Medicines List (EML)[3]. Treatment with these four proven medications (together with smoking cessation) prevents or postpones approximately 75-80% of recurrent vascular events and their complications, such as death and disability[4].

Unfortunately, there is abundant evidence that the worldwide adherence to these cardiovascular medications in patients with ASCVD is far from ideal. Less than half of patients with known ASCVD disease in high-income countries are receiving this group of cardiovascular medications, and the situation is much worse in LMICs. The PURE study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types of cardiovascular drugs[5].

A wide range of socio-economic and service level factors influence whether patients obtain medications, including the availability of medication (drugs out of stock), the lack of affordable medication and service factors, such as the availability and training of health care providers. Adherence to medication focuses on whether patients take the prescribed medication. Two recent systematic reviews on patient factors that affect adherence to ASCVD medications in secondary prevention showed that these factors go far beyond simply "forgetting" to take the medication and include a range of factors, including patients' perceptions of the cause and prognosis of the illness (e.g., fatalistic perceptions or absence of symptoms) and/or the risks and benefits of medications (e.g., fear of side effects or concern about multiple medications), the patient-physician relationship, availability of family/social network support, and comorbidities (e.g., depression)[6 7].

A recent systematic review from RCTs on interventions to improve adherence to medications in patients with ASCVD demonstrated several potential interventions, and importantly, simple interventions may be as effective as complex ones (and therefore easier to replicate)[8]. However, this review also highlighted many limitations in the current evidence, such as risk of bias, small sample sizes and lack of studies in LMICs, where most of the patients with ASCVD live. Among the most promising simple strategies to increase adherence, this review singled out Short Message Service (SMS) interventions.

Mobile phones have become an "essential" instrument of daily life worldwide, with approximately 7 billion subscribers, of whom 78% are based in LMICs[9]. This use makes mobile phones an "ideal instrument" to deliver health behaviour change interventions to large numbers of people at a low cost. Systematic reviews of RCTs using mHealth interventions confirm that SMS can be successful in changing behaviour, including smoking cessation and improved adherence to HIV medications[10,11]. Patient factors influencing adherence, such as knowledge attitudes and beliefs, could be amenable to change using mobile phone messages sent to patients.

A recent Cochrane review evaluated the effects of SMS on adherence to medications in patients with ASCVD[12]. The review identified seven trials (1310 participants) and showed a beneficial effect of SMS on adherence to medications in six of these trials. However, the quality of the evidence was very low. The Cochrane review identified the following limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV) most studies recruited only patients with acute coronary

syndrome, which leaves out an important group of patients with other arterial occlusive events (e.g., ischaemic stroke, peripheral vascular disease and programmed coronary revascularizations) who should be amenable for this type of intervention; (V) few studies were performed in LMICs; and (VI) most trials did not describe the processes behind the SMS content generation, and the few trials that did report these processes did not target the key knowledge and attitudinal factors that are known to influence adherence to medication; instead the interventions were simple "reminders".

In conclusion, given the high prevalence of people with ASCVD in LMICs and the low use of cost-effective secondary prevention medications, a low-cost intervention that builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to improve public health. The current evidence shows that SMS interventions based on behaviour-change techniques are a potentially effective strategy to increase adherence to medications in people with ASCVD. However, further large trials are needed.

To provide the high-quality evidence needed to assess the effect of SMS interventions based on behaviour-change techniques to increase adherence to medications in patients with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the efficacy and safety of SMS on adherence to cardiovascular medications. The trial is being performed in a setting (Colombia) where patient factors, such as knowledge, attitudes and beliefs, are important determinants of adherence. In this context, medicines are widely available and generally affordable, so an intervention delivered to patients via SMS has the potential to be effective.

METHODS AND ANALYSIS

This protocol is reported following the SPIRIT Standard Protocol Items recommendations for Interventional Trials[13].

Aim and objectives

The primary objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobiles phones to improve adherence to cardiovascular medications in patients with atherosclerotic cardiovascular disease (ASCVD). We will assess the intervention efficacy via the measurement of blood serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as

an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart rate as an indicator of adherence to beta-blockers.

The secondary objective is to assess the impact of mobile text messaging on adherence to medications, hospitalizations, and the composite end-point of incident Major Adverse Cardiovascular Events (MACE) at 12 months.

Choice of comparator

The trial design is a two-parallel arm in which the comparator is a control follow up. Patients allocated to the control group will receive monthly messages that convey the gratitude of the research team for their participation and emphasize the importance of follow up. The choice of comparator was guided by considerations of enhancing acceptability of the trial and enhancing retention and follow-up rates, while not materially altering medication-taking behaviours or causing participants harm or discomfort. Participants will be told that they could be allocated to one of two different groups. Furthermore, our intervention will not interfere with medical treatment. Patients will be warned that the study does not replace medical assistance and that they must continue with their traditional treatment.

Trial design

Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled trial. This design is aimed to minimize any potential bias that affects the internal validity of the study. The selection criteria were designed to increase the number of potential beneficiaries of the intervention and to keep the selection process as close as possible to the future scenario in which the intervention will be implemented. Therefore, Txt2THeart-Colombia is pragmatic in design. The active intervention will be the SMS delivered to mobile phones, and the content of the SMS is aimed to modify behaviours associated with poor adherence to ASCVD medications in ASCVD patients. Randomization will be performed as block randomization with a 1:1 allocation.

Study setting

We will recruit patients at Fundación Cardiovascular in Colombia, which has a staff that is knowledgeable in trials and a sufficient pool of eligible patients. The trial will continue to add sites, if necessary, to ensure that the sample size is achieved. There is no limit to the maximum number of patients to be recruited in each site.

Eligibility criteria

Inclusion criteria: Adult patients ≥18 years old with a history of at least one of the following arterial occlusive events will be included: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischaemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Patients should receive cardiovascular medication treatment at the moment of recruitment. Patients should own a mobile phone and be able to read SMS.

Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular secondary prevention medications.

Intervention

The intervention under evaluation consists of *behavioural change techniques* (BCTs) delivered via SMS. We developed our intervention following the recommendations of Abroms et al[14]. First, we reviewed the literature on individual level factors that influence adherence to medication. We performed country-specific qualitative studies using focus group discussions and semi-structured interviews to evaluate cardiovascular patients' perceptions about mHealth programmes to determine the necessary content and preferred timing and frequency of the SMS messages. To construct the content of the SMS, we wrote messages using educational and enabling behaviour change functions and established BCTs to target the potentially modifiable factors that influence the adherence referred to in the literature and found in our qualitative studies[15]. Finally, we tested the SMS messages with participants and adapted the messages based on their feedback to ensure the messages were understandable, acceptable, and relevant[16]. The resultant intervention delivered by SMS provides information about health consequences of adherence or non-adherence, instruction on how to take medication, medicine-taking prompts and cues, support in establishing medicine-taking habits, reframing medicine-taking and provides or encourages social support for taking medication. The messages were designed according to the Transtheoretical Model (TTM) (Prochaska & DiClemente, 1992) and were aimed to enhance actions related to the steps and processes of this model. We will send messages daily the first month, three times per week the second month and once weekly the last ten months. This reducing frequency is consistent with the TTM, which suggests that people in the early stages of change require more intense input than people in later stages. In accordance with data from the focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The intervention will be delivered through an electronic platform, and it will

be a one-way intervention. Due to a lack of economic resources, we will not tailor the messages. The trial intervention will start the day after recruitment and continue for 12 months or until the participant withdraws from the study or dies. The follow-up duration will be at least 12 months to a maximum of 36 months. Participants will not receive messages after month 12.

Outcomes

The primary outcomes were selected for their clinical relevance and differences in changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of adherence to statins, *systolic blood pressure* as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and *heart rate* as an indicator of adherence to beta-blockers.

The following secondary outcomes will be included: *Urine levels of 11 dhTxB2* as an indicator of adherence to antiplatelet therapy; *adherence to cardiovascular medications* used in secondary prevention as measured using the MARS-5 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular disease and non-cardiovascular death or hospitalizations due to non-cardiovascular disease. We will also include road traffic crashes (the only potential known hazard of text messaging) and death due to all causes as secondary outcomes.

Participant timeline

Participants who fulfil the eligibility criteria and provide their informed consent will be recruited into the txt2heart trial. After the participant provided informed consent, baseline characteristics will be collected at the first visit using questionnaires (MARS-5 and PHQ-9 Patient Health Questionnaire), blood samples, blood pressure, and heart rate. Participants will be randomized to the intervention or control arm. The trial intervention will start the day after recruitment and will continue for 12 months to a maximum of 36 months, or when the participant withdraws from the study, or dies. We will perform a phone follow-up interview three months later, during the second visit, to evaluate adequate SMS delivery and the occurrence of clinical events. Finally, we will collect data on adherence to cardiovascular medications (MARS-5), blood pressure, heart rate and clinical end-points in the third visit (12 months later). The 12-month follow up marks the primary outcome point. For patients with follow up beyond 12 months, we will perform (by phone) assessments of clinical outcomes (death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome,

nonfatal stroke, or urgent revascularization) every 6 months until 36 months, the longest available follow-up (figure 1).

Figure 1.

Trial flowchart

Sample Size

The sample size of the study is 1600 participants. The power of the study was calculated for differences between arms in the reduction in the primary outcome LDL-C (12-month minus baseline).

The power of the study was calculated for the primary outcomes of the clinical trial, i.e., differences in the levels of physiological markers of adherence to cardiovascular drugs. Because the power of a sample size depends on several parameters in this study, such as the doses are finally prescribed to patients and what proportion of patients will adhere, we performed several power and sample size calculations for different scenarios. We concluded that 1600 was a reasonable sample size. For example, assuming that adherent patients to 40 mg atorvastatin for 12 months are expected to have an average LDL-cholesterol reduction of 91.3 mg/dL (data derived from randomized clinical trials), and non-adherent patients will reduce LDL-cholesterol by an average of 18.3 mg/dL (or 20% of the reduction in adherent patients) and that the standard deviation of the changes is approximately 27.07 ml/dL, we would have 97% power to detect a 7% difference in adherence between arms or a 77% power to detect a 5% difference (always using a 5% type-I error). However, if patients were on 20 mg atorvastatin and the expected reductions in LDL-C were 80.05 mg/dL in adherent and 16.01 mg/dL in non-adherent patients, then we would have a 91% power to detect a 7% difference of adherence between arms and a 66% power to detect a 5% difference between arms (table 1).

Table 1

Sample size calculations

Statins and its frequency in trials		Reduction in LDL after a year of treatment in adherents and non-adherents			Power to detect differences depending on adherence increase		
	%	**AD=yes**	**AD=No**	**Dif**	**5.0%**	**7.0%**	**10.0%**
Atorvastatin 10	1.5%	1.79	0.36	1.43	53%	82%	98%
Atorvastatin 20	32.9 %	2.07	0.41	1.66	66%	91%	100%

Atorvastatin 40	52.4 %	2.36	0.47	1.89	77%	97%	100%
Atorvastatin 80	9.4%	2.64	0.53	2.11	85%	99%	100%
Fluvastatin 20 mg	0.0%	1.02	0.20	0.82	21%	37%	64%
Lovastatin 40	0.0%	1.77	0.35	1.42	53%	81%	98%
Pravastatin 10	0.0%	0.95	0.19	0.76	19%	33%	58%
Pravastatin 20	0.0%	1.17	0.23	0.94	27%	46%	76%
Pravastatin 40	0.0%	1.38	0.28	1.10	35%	60%	88%
Rosuvastatin 5	0.0%	1.84	0.37	1.47	56%	84%	99%
Rosuvastatin 10	0.3%	2.08	0.42	1.66	66%	91%	100%
Rosuvastatin 20	1.7%	2.32	0.46	1.86	76%	96%	100%
Rosuvastatin 40	1.6%	2.56	0.51	2.05	83%	98%	100%
Simvastatin 10	0.0%	1.31	0.26	1.05	32%	55%	85%
Simvastatin 20	0.1%	1.54	0.31	1.23	42%	69%	94%
Simvastatin 40	0.2%	1.78	0.36	1.42	53%	81%	98%
Simvastatin 80	0.0%	2.01	0.40	1.61	63%	90%	100%

*Elaborated by the authors

Power is calculated assuming a sample size of 800 per arm, 5% type-I error, a standard deviation of LDL change of 0.7 and that non-adherent patients will still reduce their LDL on average 20% of the reduction in adherent patients.

Interpretation of the table: Example of third line (atorvastatin 40): 52.4% of patients in the hospital take atorvastatin 40. Adherent patients are expected to reduce their cholesterol an average of 2.36 mmol/l in the first year, and non-adherent patients are expected to reduce it 0.47 mmol/l. If all patients were on atorvastatin 40, we would have a 77% power to detect a true increase in adherence of 5%, a 97% power to detect a true increase in adherence of 7% and almost a 100% power to detect a true increase in adherence of 10%. Atorvastatin is the most prescribed statin in patients in our study. About the 65% of the sample use.

Recruitment

The pragmatic nature of this trial will allow collaborators to follow different strategies for participant recruitment according to the setting. There are three main approaches for the recruitment of patients who fulfil the inclusion criteria a) in hospital patients at the time of discharge, b) patients attending outpatient clinics, c) and patients who are in the health care facility database and who will be contacted by phone calls and recruited in outpatient clinics.

Assignment of intervention

Randomization: We will use block randomization (varying size), stratifying by centre and with 1:1 allocation between the intervention and control arm. Randomization will be performed centrally using the CommCare platform after eligibility criteria was confirmed, informed consent signed, and baseline information collected. Therefore, the randomized allocation will not be revealed until after a participant was formally entered into the trial. Therefore, concealment of allocation will be complete. The SMS will be automatically generated by the CommCare platform and unknown to the investigators in contact with patients.

Blinding: Because of the nature of the intervention (SMS messages), it is not possible to include blind participants. However, the tx2theart trial will perform a blinded assessment of outcomes. Research personnel collecting data on clinical events, adherence scales, and biomarkers will not have access to treatment allocation. The laboratory results will be performed once trial follow-up is completed.

Data collection methods

Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered in the CommCare platform, designed by Dimagi. CommCare is an open source mobile platform designed for data collection, client management, decision support, and behaviour change communication. The electronic devices (desktop computers, laptops and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by Fundación Cardiovascular de Colombia.

Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while maximizing retention to follow-up. The following strategies to prevent loss to follow-up will be used. 1) One phone call at the third month of participation. Trained personnel different from the other interviewers will phone the participants to guarantee the blind design. Professionals in charge of the follow-up are trained in patient contact with the ability to empathize with volunteers. 2) We will register at least three relatives' numbers to contact in case we are not able to reach the patient, and we will phone the participant's relatives. 3) We will register the addresses of participants in case we cannot reach the patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the participants a contact phone number to let us to know if they change their phone number contact. We will explain these strategies to participants to get permission for further contact.

Clinical outcomes

Death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization will be defined by local investigators based on clinical notes and clear objective criteria using the suggestions provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials[17].

Self-reported adherence

To estimate adherence, we will use a self-reported scale named Medication Adherence Report Scale 5 (MARS-5), which is a valid and reliable scale for measuring adherence to medication in chronic conditions at trial entry and at the final assessment at 12 months[18]. The MARS-5 Scale elicits patients' reports of non-adherence. To diminish the social pressure on patients to report high adherence, items are phrased in a non-threatening manner, and patients are assured that their responses will be anonymous and confidential. Participants are asked to rate the frequency with which they engaged in each of five aspects of non-adherent listed behaviours (e.g., 'I forget to take these medicines', 'I stop taking these medicines for a while') using a 5-point scale ranging from 'never' to 'always'. Scores for each item are summed to give a total score that ranged from 5 to 25, with higher scores indicating higher levels of adherence.

Biomarkers

Physiological measurements of heart rate and blood pressure will be measured using a calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by trained health care professionals. Patients will sit quietly for 10 minutes before the examinations.

Blood LDL-C: Quantification of serum LDL will be performed using automated equipment by a direct method.

Recent large epidemiological studies confirmed that resting heart rate is an independent predictor of cardiovascular mortality. Heart rate decrease is itself an important mechanism of the benefit of the blockers and other drugs that reduce heart rate after an acute myocardial infarction (1–4). Controversies on the optimal dose to obtain results remain, but the reduction in heart rate is notorious in patients receiving beta-blockers (5). In Colombia, beta-blockers are a first-line drug used for secondary prevention. The most frequently beta-blocker is carvedilol, which exhibits advantages in decreasing heart rate and mortality in patients with some type of cardiovascular event (6).

Data management

Data will be stored on a secure system and will be password protected. All trial procedures will be performed in accordance with the principles of Good Clinical Practice (GCP). Essential documents of the sponsor/trial organizers and investigators will be retained for 15 years and at least 10 years after completion of the trial. The research staff will maintain appropriate medical and research records for this clinical study and meet with the regulatory and institutional frameworks for the protection of the confidentiality requirements. As sponsor of this trial, Fundación Cardiovascular de Colombia will allow regulatory agencies to examine (under applicable law) clinical records to check the quality, safety and progress of the study.

Statistical Analysis

The main analyses will be an "intention to treat", meaning it will compare all patients allocated to the intervention to patients allocated to the control arm, regardless of whether they received the allocated intervention. A sensitivity per protocol analysis will also be performed. For continuous outcomes (including all primary outcomes: LDL cholesterol, blood pressure and Heart rate), we will estimate an ANCOVA model regressing the 12-month difference from baseline in the allocated group and the mean centred baseline values of the continuous variable. Deaths and hospitalizations will be analysed using Cox regression models to estimate hazard ratios. The assumptions underlying all of these models will be assessed. For subgroup analyses, we will only consider a limited number of variables that, given the mechanism of action of the intervention, could modify the effect of the intervention. A detailed statistical analysis plan setting out full details of the proposed analyses will be prepared and completed before the trial database is locked for final analysis. Missing data will be managed by an intention to treat analysis.

Data Monitoring

Data monitoring will be executed according to GCP Guidelines. This trial is a large, pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change behaviour and increase adherence of safe and proven effective interventions for secondary prevention that have been in clinical use for decades. Clinical management for underlying conditions will remain as per hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring because of participation in this research study was assessed as low risk to participants in each of these categories. Based on the low risks associated with this trial, there will not be a data monitoring committee. However, a monitoring plan to ensure appropriate performance of the trial will be developed, which will

incorporate 100% central monitoring in conjunction with procedures, such as investigator training and meetings and written guidance. All data will be subject to statistical monitoring, and at least 10% of data will be subjected to on-site monitoring. Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for 15 years after the end of the trial.

Indirect Patient and Public Involvement

We did not directly include PPI in this study. However, to design the intervention, we interviewed patients about their perceptions of e-health and their previous experience with mobile cellular phone technology. The Ethics Committee evaluated and approved our research included patient representatives.

ETHICS AND DISSEMINATION

Protocol amendments

The protocol for the trial has not been modified.

Ethical considerations

The study will be performed in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki.

Ethical approval

The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial.

Informed Consent:

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient will be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. Written consent must be given by the patient and/or the legal guardian of the patient after detailed information about the study is provided in accordance with any national provisions on the protection of clinical study patients. The verbal explanation will cover all of the elements specified in the written information provided to the patient. Patients and/or legal guardians will be

required to sign and date the informed consent form. Patients who refuse to give or who withdraw written informed consent will not be included or continue in the study. The trial will include a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or law of protection of personal data, where the study team is authorized to handle personal and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be recorded and stored for a set time. Eligible participants will only be included in the study after signing “Txt2Heart-Colombia” informed consent (testified, where required by law or regulation), as approved by the ethics committees. The process will be documented in the patient source documents, specifically in CRFs (Case Report Form).

Confidentiality: Information about the study subjects will be kept confidential. The investigators will ensure the anonymity of patients, and patients will not be identified by name in any document. Informed consent forms and patient recruitment registration will be kept strictly confidential only to permit identification of the patient at Fundación Cardiovascular de Colombia. Information about the study subjects will be handled under the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law of data protection). The regulations that require an authorization signed by the patient including the follow information: What protected health information (PHI) will be collected from the study subjects, who will have access to that information and why, who will use and disclose that information and the right to withdraw his/her authorization to use their PHI.

Access to data

The principal investigator and sub-investigators will have access to the data to verify and analyse the results. To ensure confidentiality, all of the investigators will be blinded of participant identification.

Ancillary and post-trial care

Due to its low risk, the intervention in this trial will not include insurance for participants. However, we will refer patients to their medical services in case we think that they need assistance. Furthermore, a full explanation of the scope and limitations of the study will be told to the patients before they sign the informed consent.

Dissemination policy

The Txt2heart Colombia trial is aimed to provide high level evidence that evaluates whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the health local authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

The results from the trial will be published in an open journal to provide scientists, clinicians and policymakers access to the data.

REFERENCES

1. Perel, P., et al., *Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease.* Glob Heart, 2015. **10**(2): p. 99-110.
2. Perel, P., et al., *Noncommunicable diseases and injuries in Latin America and the Caribbean: time for action.* PLoS Med, 2006. **3**(9): p. e344.
3. World Health Organization. *Model List of Essential Medicines (20th List)*. 2017 [cited [Accessed June 23 2017]; Available from: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.
4. Yusuf, S., *Two decades of progress in preventing vascular disease.* Lancet, 2002. **360**(9326): p. 2-3.
5. Yusuf, S., et al., *Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey.* Lancet, 2011. **378**(9798): p. 1231-43.
6. Rashid, M.A., et al., *Medication taking in coronary artery disease: a systematic review and qualitative synthesis.* Ann Fam Med, 2014. **12**(3): p. 224-32.
7. R.M., *Patient factors that influence cardiovascular medication adherence (MSc Thesis)*. 2014, London School of Hygiene & Tropical Medicine.
8. Santo, K., et al., *Interventions to improve medication adherence in coronary disease patients: A systematic review and meta-analysis of randomised controlled trials.* Eur J Prev Cardiol, 2016. **23**(10): p. 1065-76.
9. International Telecommunications Union. *ICT Facts and figures*. 2014 [cited [Accessed July 20, 2017]; Available from: http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2014-e.pdf.
10. Free, C., et al., *The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review.* PLoS Med, 2013. **10**(1): p. e1001362.
11. Catalani, C., et al., *mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature.* Open AIDS J, 2013. **7**: p. 17-41.
12. Adler, A.J., et al., *Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2017. **4**: p. Cd011851.

13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Abroms, L.C., et al., *Developing and Pretesting a Text Messaging Program for Health Behavior Change: Recommended Steps.* JMIR Mhealth Uhealth, 2015. **3**(4): p. e107.
15. Michie, S., et al., *The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions.* Ann Behav Med, 2013. **46**(1): p. 81-95.
16. Moore, G.F., et al., *Process evaluation of complex interventions: Medical Research Council guidance.* BMJ, 2015. **350**: p. h1258.
17. Hicks, K.A., et al., *2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards).* Circulation, 2015. **132**(4): p. 302-61.
18. Mahler, C., et al., *Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany.* J Eval Clin Pract, 2010. **16**(3): p. 574-9.

Authors' contributions

Study director

Norma Cecilia Serrano Díaz, MSc: Senior researcher and Research Department Director at Fundación Cardiovascular de Colombia. Dr Serrano participated in choosing of the biomarkers and the processing design for the biological samples.

Principal investigator

Anderson Bermon Angarita, MSc: Junior researcher and epidemiologist at Fundación Cardiovascular de Colombia. Dr. Bermon participated in the trial design and studied the impact of the results in Colombia, considering the healthcare system limitations.

Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor Faculty of Psychology, Pontificia Bolivariana University. Dr. Uribe designed the message intervention and studied the behavioural theories that support the intervention methodology.

Study chair

Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University College London at Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas conceived the idea of conducting the trial and participated in the methodology design of the trial.

Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived the idea of conducting the trial and participated in the methodology design of the trial.

Sub-investigators:

Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research Department of Primary Care and Population Health, University College London. Dr. Murray contributed in the intervention design and message validity process.

David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the statistical analysis and data management of the trial.

Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and participated in the validity process of the message intervention.

Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins contributed in the message intervention design.

Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of Pharmacy, University College London. Dr. Horne participated in the validity process of the message intervention and choosing adherence scales.

Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the processing design for biological samples.

Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.

Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez participated in the intervention design.

Acknowledgments statement

We thank the Cardiology Department medical staff at Fundación Cardiovascular de Colombia for their help with developing our research questions.

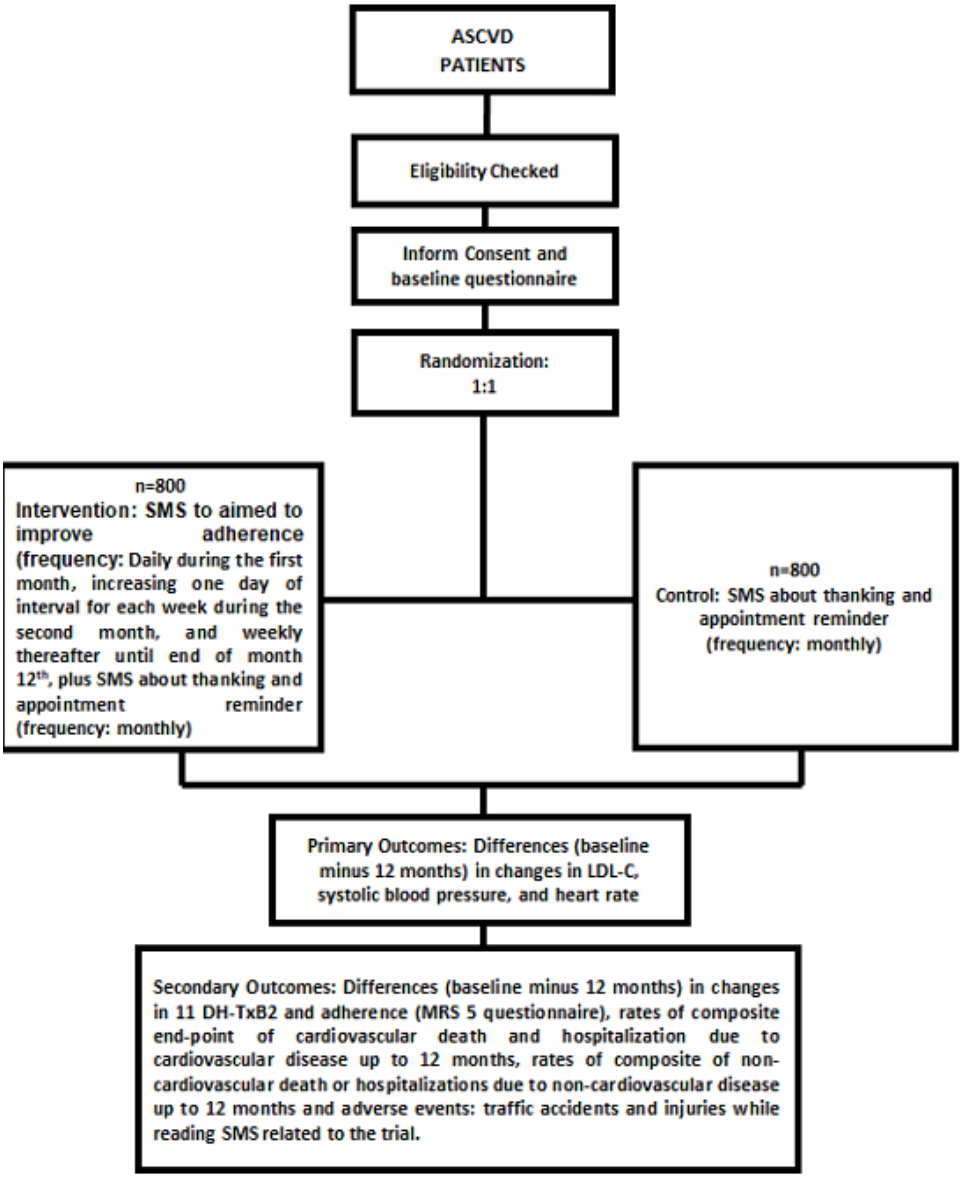
Funding statement

This work was supported by COLCIENCIAS code 656672553352 grant 899-2015

Fundación Cardiovascular de Colombia, Floridablanca
London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded Reference MR/N021304/1
Universidad Pontificia Bolivariana, Bucaramanga sectional

Competing interests' statement

All authors declare there is not conflict of interest.
All funding institutions declare there is not conflict of interest.


ASCVD PATIENTS
Eligibility Checked
Inform Consent and baseline questionnaire
Randomization: 1:1
n=800
Intervention: SMS to aimed to improve adherence (frequency: Daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th, plus SMS about thanking and appointment reminder (frequency: monthly)
n=800
Control: SMS about thanking and appointment reminder (frequency: monthly)
Primary Outcomes: Differences (baseline minus 12 months) in changes in LDL-C, systolic blood pressure, and heart rate
Secondary Outcomes: Differences (baseline minus 12 months) in changes in 11 DH-TxB2 and adherence (MRS 5 questionnaire), rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months, rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months and adverse events: traffic accidents and injuries while reading SMS related to the trial.

Flowchart

Supplementary file

Trial Summary

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT03098186
Date of registration in primary registry	March 10, 2017
Source(s) of monetary or material support	Departamento Administrativo de Ciencia, Tecnología e Innovación Colombia COLCIENCIAS Fundación Cardiovascular de Colombia London School of Hygiene and Tropical Medicine University College, London Universidad Pontificia Bolivariana
Primary sponsor	COLCIENCIAS Contact: contacto@colciencias.gov.co (+57) (1) 6258480 ext. 2081
Secondary sponsor (s)	Fundación Cardiovascular de Colombia
Contact for public queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Contact for scientific queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Public title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol
Scientific title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Countries of recruitment	Colombia
Health condition(s) or problem(s) studied	Acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation) Stable angina Ischemic cerebrovascular disease Peripheral arterial disease
Interventions	Active treatment: will consist of SMS that are aimed to modified behavioural factors associated with poor adherence to cardiovascular medications used in secondary prevention. The SMS will be delivered daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th. In addition, they will receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly. Control: participants will only receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly.
Key inclusion and exclusion criteria	Inclusion Criteria: Age ≥18 years old Sexes eligible for study: both History of at least one of the following arterial occlusive events: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Own at least one mobile phone

	Ability to read and understand text messages (SMS) Intention to stay in the country of recruitment during the next 12 months Exclusion Criteria: Contraindication to take all cardiovascular medications used in secondary prevention. Participation in another randomized clinical trial that could interfere with adherence to treatment.
Study type	Two-parallel arm, only-blind, individually randomized controlled trial.
Date of first enrolment	April 2017
Target sample size	1600
Recruitment status	Recruiting
Primary outcome(s)	Differences in changes (baseline minus 12 months) of: Low density lipoprotein cholesterol (LDL-C) Systolic Blood pressure Heart Rate
Key secondary outcomes	Differences in the changes (baseline minus 12-months) of: (i) Adherence to cardiovascular medications used in secondary prevention measured by MARS-5 questionnaire; and (ii) Urinary levels of 11 dh-TxB2. Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months. Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months Adverse events: traffic accidents and injuries while reading SMS related to the trial.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#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	18
Roles and responsibilities: committees	#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)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies	5

		(published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	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, non-inferiority, exploratory)	7
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	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)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	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)	9
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	11

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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	12
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	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	13

		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	
Data collection plan: retention	#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	13
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	14
Statistics: outcomes	#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	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#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)	14
Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15

formal committee		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	
Data monitoring: interim analysis	#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	15
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
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)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
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	16
Dissemination policy: trial results	#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	17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	17

reproducible research		participant-level dataset, and statistical code	
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16
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	13

BMJ Open

Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028017.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Aug-2019
Complete List of Authors:	Bermon Angarita, Anderson; Fundacion Cardiovascular de Colombia, Research; CES University Uribe Rodríguez, Ana; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Pérez-Rivero, Paula; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Prieto-Merino, David; London School of Hygiene & Tropical Medicine Cáceres Rivera, Diana ; Universidad Cooperativa de Colombia, Nursing Guio, Elizabeth; Fundacion Cardiovascular de Colombia, Metabolism and Genoma Laboratory Atkins, Louise; University College London Research Department of Epidemiology and Public Health Horne, Robert; University College London Murray, Elizabeth; University College London, Primary Care and Population Health Serrano Díaz, Norma; Fundación Cardiovascular de Colombia, Direction of research Free, Caroline; London School of Hygiene and Tropical Medicine, Public Health interventions Unit Perel, Pablo; LSHTM, EPH Casas, Juan Pablo ; University College London Medical School, Clinical Epidemiology and Informatics ; Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Research
Primary Subject Heading:	Public health
Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: The Txt2heart-Colombia randomized controlled trial protocol

Anderson Bermon*
Fundación Cardiovascular de Colombia
Research department
Av. 5 # 6-33, Floridablanca, Santander, Colombia.
Postal code: 681004
Telephone number: (+57) 3002053041
FAX: (+57) 6796470
andersonbermon@fcv.org
*Corresponding author

Ana Fernanda Uribe Rodríguez
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

Paula Fernanda Pérez-Rivero
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

David Prieto-Merino
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine
London, UK

Diana Isabel Cáceres Rivera
Cooperativa Colombia University
Faculty of Nursing
Bucaramanga, Santander, Colombia

Elizabeth Guio
Metabolism and Genome Laboratory
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Lou Atkins
Faculty of Health Psychology
University College London
London, UK.

Robert Horne
Centre for Behavioural Medicine
UCL School of Pharmacy
University College London
London, UK.

Elizabeth Murray
Research Department of Primary Care and Population Health
University College London

London, UK.

Norma Cecilia Serrano Díaz
Research Department
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Caroline Free
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Pablo A. Perel
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Juan P. Casas
Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
VA Boston Healthcare System
Boston, Massachusetts, USA.

Keywords: Cardiovascular diseases, Health behavior, Medications adherence, mHealth, text messaging

Word count: 5006

Abstract

Introduction: Anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that adherence to these cardiovascular medications is far from ideal. A recent Cochrane review showed a potential beneficial effect of SMS interventions on adherence to medication in ASCVD patients.

Methods and analysis: The Txt2heart study is a pragmatic randomized single-blind controlled trial. The objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobile phones to improve adherence to cardiovascular medications in patients with ASCVD. The intervention consists of behavioural techniques delivered via SMS. The primary outcomes are changes in blood serum low-density lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins, systolic blood pressure as an indicator of adherence to blood-lowering therapies and heart rate as an indicator of adherence to beta-blockers. Secondary outcomes will include urine levels of **11**-dehydrothromboxane B2 (11dhTxB2), self-reported adherence to cardiovascular medications and rates of cardiovascular death or hospitalization due to cardiovascular disease.

Ethics and dissemination: The study will be performed in compliance with the protocol, regulatory requirements, Good Clinical Practice and ethical principles of the Declaration of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to

evaluate whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the local health authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

Trial registration number: ClinicalTrials.gov: NCT03098186

Strengths and limitations of this study.

The trial uses an innovative intervention through SMS methodology based on behaviour theories.

The trial uses biomarkers to evaluate medication adherence.

The trial is the largest evaluating SMS to increase adherence for cardiovascular secondary prevention

Measuring adherence is challenging; we are triangulating data from biomarkers and self-reported adherence to improve the accuracy of the trial measure of effect

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death worldwide. Approximately 35 million people worldwide have an acute coronary event or cerebrovascular event annually, and one quarter of these events occur in people with established ASCVD[1]. These arterial occlusive events occur at an early age in low and middle-income countries (LMICs), which affects economically active populations and results in large economic impacts[2].

Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the risk of ASCVD events in patients with established ASCVD, and these agents are included in the list of the World Health Organization (WHO) Essential Medicines List (EML)[3]. Treatment with these four proven medications (together with smoking cessation) prevents or postpones approximately 75-80% of recurrent vascular events and their complications, such as death and disability[4].

Unfortunately, there is abundant evidence that the worldwide adherence to these cardiovascular medications in patients with ASCVD is far from ideal. Less than half of patients with known ASCVD disease in high-income countries are receiving this group of cardiovascular medications, and the situation is much worse in LMICs. The PURE

study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types of cardiovascular drugs[5].

A wide range of socio-economic and service level factors influence whether patients obtain medications, including the availability of medication (drugs out of stock), the lack of affordable medication and service factors, such as the availability and training of health care providers. Adherence to medication focuses on whether patients take the prescribed medication. Two recent systematic reviews on patient factors that affect adherence to ASCVD medications in secondary prevention showed that these factors go far beyond simply "forgetting" to take the medication and include a range of factors, including patients' perceptions of the cause and prognosis of the illness (e.g., fatalistic perceptions or absence of symptoms) and/or the risks and benefits of medications (e.g., fear of side effects or concern about multiple medications), the patient-physician relationship, availability of family/social network support, and comorbidities (e.g., depression)[6 7].

A recent systematic review from RCTs on interventions to improve adherence to medications in patients with ASCVD demonstrated several potential interventions, and importantly, simple interventions may be as effective as complex ones (and therefore easier to replicate)[8]. However, this review also highlighted many limitations in the current evidence, such as risk of bias, small sample sizes and lack of studies in LMICs, where most of the patients with ASCVD live. Among the most promising simple strategies to increase adherence, this review singled out Short Message Service (SMS) interventions.

Mobile phones have become an "essential" instrument of daily life worldwide, with approximately 7 billion subscribers, of whom 78% are based in LMICs[9]. This use makes mobile phones an "ideal instrument" to deliver health behaviour change interventions to large numbers of people at a low cost. Systematic reviews of RCTs using mHealth interventions confirm that SMS can be successful in changing behaviour, including smoking cessation and improved adherence to HIV medications[1011]. Patient factors influencing adherence, such as knowledge attitudes and beliefs, could be amenable to change using mobile phone messages sent to patients.

A recent Cochrane review evaluated the effects of SMS on adherence to medications in patients with ASCVD[12]. The review identified seven trials (1310 participants) and showed a beneficial effect of SMS on adherence to medications in six of these trials. However, the quality of the evidence was very low. The Cochrane review identified the following limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV) most studies recruited only patients with acute coronary syndrome, which

leaves out an important group of patients with other arterial occlusive events (e.g., ischaemic stroke, peripheral vascular disease and programmed coronary revascularizations) who should be amenable for this type of intervention; (V) few studies were performed in LMICs; and (VI) most trials did not describe the processes behind the SMS content generation, and the few trials that did report these processes did not target the key knowledge and attitudinal factors that are known to influence adherence to medication; instead the interventions were simple "reminders".

In conclusion, given the high prevalence of people with ASCVD in LMICs and the low use of cost-effective secondary prevention medications, a low-cost intervention that builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to improve public health. The current evidence shows that SMS interventions based on behaviour-change techniques are a potentially effective strategy to increase adherence to medications in people with ASCVD. However, further large trials are needed.

To provide the high-quality evidence needed to assess the effect of SMS interventions based on behaviour-change techniques to increase adherence to medications in patients with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the efficacy and safety of SMS on adherence to cardiovascular medications. The trial is being performed in a setting (Colombia) where patient factors, such as knowledge, attitudes and beliefs, are important determinants of adherence. In this context, medicines are widely available and generally affordable, so an intervention delivered to patients via SMS has the potential to be effective.

METHODS AND ANALYSIS

This protocol is reported following the SPIRIT Standard Protocol Items recommendations for Interventional Trials[13] (see supplementary file 1).

Aim and objectives

The primary objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobiles phones to improve adherence to cardiovascular medications in patients with atherosclerotic cardiovascular disease (ASCVD). We will assess the intervention efficacy via the measurement of blood serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as

an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart rate as an indicator of adherence to beta-blockers.

The secondary objective is to assess the impact of mobile text messaging on self-reported adherence to medications, hospitalizations, and the composite end-point of incident Major Adverse Cardiovascular Events (MACE) at 12 months.

Choice of comparator

The trial design is a two-parallel arm in which the comparator is a control follow up. Patients allocated to the control group will receive monthly messages that convey the gratitude of the research team for their participation and emphasize the importance of follow up. The choice of comparator was guided by considerations of enhancing acceptability of the trial and enhancing retention and follow-up rates, while not materially altering medication-taking behaviours or causing participants harm or discomfort. Participants will be told that they could be allocated to one of two different groups. Furthermore, our intervention will not interfere with medical treatment. Patients will be warned that the study does not replace medical assistance and that they must continue with their traditional treatment.

Trial design

Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled trial. This design is aimed to minimize any potential bias that affects the internal validity of the study. The selection criteria were designed to increase the number of potential beneficiaries of the intervention and to keep the selection process as close as possible to the future scenario in which the intervention will be implemented. Therefore, Txt2THeart-Colombia is pragmatic in design. The active intervention will be the SMS delivered to mobile phones, and the content of the SMS is aimed to modify behaviours associated with poor adherence to ASCVD medications in ASCVD patients. Randomization will be performed as block randomization with a 1:1 allocation.

Study setting

We will recruit patients at Fundación Cardiovascular in Colombia, which has a staff that is knowledgeable in trials and a sufficient pool of eligible patients. The trial will continue to add sites, if necessary, to ensure that the sample size is achieved. There is no limit to the maximum number of patients to be recruited in each site.

Eligibility criteria

Inclusion criteria: Adult patients ≥18 years old with a history of at least one of the following arterial occlusive events will be included: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischaemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).. Patients should own a mobile phone and be able to read SMS.
Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular secondary prevention medications.

Intervention

The intervention under evaluation consists of *behavioural change techniques* (BCTs) delivered via SMS. We developed our intervention following the recommendations of Abroms et al[14]. First, we reviewed the literature on individual level factors that influence adherence to medication. We performed country-specific qualitative studies using focus group discussions and semi-structured interviews to evaluate cardiovascular patients' perceptions about mHealth programmes to determine the necessary content and preferred timing and frequency of the SMS messages. To construct the content of the SMS, we wrote messages using educational and enabling behaviour change functions and established BCTs to target the potentially modifiable factors that influence the adherence referred to in the literature and found in our qualitative studies[15]. Finally, we tested the SMS messages with participants and adapted the messages based on their feedback to ensure the messages were understandable, acceptable, and relevant[16]. The resultant intervention delivered by SMS provides information about health consequences of adherence or non-adherence, instruction on how to take medication, medicine-taking prompts and cues, support in establishing medicine-taking habits, reframing medicine-taking and provides or encourages social support for taking medication[17]. The messages were designed according to the Transtheoretical Model (TTM) (Prochaska & DiClemente, 1992) and were aimed to enhance actions related to the steps and processes of this model. We will send messages daily the first month, three times per week the second month and once weekly the last ten months. This reducing frequency is consistent with the TTM, which suggests that people in the early stages of change require more intense input than people in later stages. In accordance with data from the focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The intervention will be delivered through an electronic platform, and it will be a one-way intervention. We will explain patients that they should not answer the messages but they will be able to request to stop receiving the messages and withdraw from the trial by sending a message with the word "STOP". We will explain to patients that they should

send the 'stop' message in this situation . Stop messages will be saved and monitored by a trained engineer, separate from the study team, in order to maintain blinding. Similarly, a trained engineer, separate from the study team, will save and monitor the patients' answers if they respond to the messages. Because of the pragmatic nature of our study we will not tailor the messages. The trial intervention will start the day after recruitment and continue for 12 months or until the participant withdraws from the study or dies. The follow-up duration will be at least 12 months to a maximum of 36 months. Participants will not receive messages after month 12.

Outcomes

The primary outcomes were selected for their clinical relevance and include: differences in changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of adherence to statins, *systolic blood pressure* as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and *heart rate* as an indicator of adherence to beta-blockers.

The following secondary outcomes will be included: *Urine levels of 11 dhTxB2* as an indicator of adherence to antiplatelet therapy; *self-reported adherence to cardiovascular medications* used in secondary prevention as measured using the MARS-5 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular disease and non-cardiovascular death or hospitalizations due to non-cardiovascular disease. We will also include road traffic crashes (the only potential known hazard of text messaging) and death due to all causes as secondary outcomes.

Participant timeline

Participants who fulfil the eligibility criteria and provide their informed consent will be recruited into the txt2heart trial. After the participant provided informed consent, baseline characteristics will be collected at the first visit using questionnaires (MARS-5 and PHQ-9 Patient Health Questionnaire), blood samples, blood pressure, and heart rate. Participants will be randomized to the intervention or control arm. The trial intervention will start the day after recruitment and will continue for 12 months to a maximum of 36 months, or when the participant withdraws from the study, or dies. We will perform a phone follow-up interview three months later, during the second visit, to evaluate adequate SMS delivery and the occurrence of clinical events. Finally, we will collect data on self-reported adherence to cardiovascular medications (MARS-5), blood pressure, heart rate and clinical end-points in the third visit (12 months later). The 12-month follow up marks the primary outcome point. For patients with follow up beyond 12 months, we

will perform (by phone) assessments of clinical outcomes (death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization) every 6 months until 36 months, the longest available follow-up (figure 1).

Figure 1.

Trial flowchart

Sample Size

The sample size of the study is 1600 participants. The power of the study was calculated for differences between arms in the reduction in the primary outcome LDL-C (12-month minus baseline).

The power of the study was calculated for the primary outcomes of the clinical trial, i.e., differences in the levels of physiological markers of adherence to cardiovascular drugs. Because the power of a sample size depends on several parameters in this study, such as the doses are finally prescribed to patients and what proportion of patients will adhere, we performed several power and sample size calculations for different scenarios. We concluded that 1600 was a reasonable sample size. For example, assuming that adherent patients to 40 mg atorvastatin for 12 months are expected to have an average LDL-cholesterol reduction of 91.3 mg/dL (data derived from randomized clinical trials), and non-adherent patients will reduce LDL-cholesterol by an average of 18.3 mg/dL (or 20% of the reduction in adherent patients) and that the standard deviation of the changes is approximately 27.07 ml/dL, we would have 97% power to detect a 7% difference in adherence between arms or a 77% power to detect a 5% difference (always using a 5% type-I error). However, if patients were on 20 mg atorvastatin and the expected reductions in LDL-C were 80.05 mg/dL in adherent and 16.01 mg/dL in non-adherent patients, then we would have a 91% power to detect a 7% difference of adherence between arms and a 66% power to detect a 5% difference between arms (table 1).

Table 1

Sample size calculations

Statins and its frequency in trials		Reduction in LDL after a year of treatment in adherents and non-adherents			Power to detect differences depending on adherence increase		
	%	**AD=yes**	**AD=No**	**Dif**	**5.0%**	**7.0%**	**10.0%**
Atorvastatin 10	1.5%	1.79	0.36	1.43	53%	82%	98%

Atorvastatin 20	32.9%	2.07	0.41	1.66	66%	91%	100%
Atorvastatin 40	52.4%	2.36	0.47	1.89	77%	97%	100%
Atorvastatin 80	9.4%	2.64	0.53	2.11	85%	99%	100%
Fluvastatin 20 mg	0.0%	1.02	0.20	0.82	21%	37%	64%
Lovastatin 40	0.0%	1.77	0.35	1.42	53%	81%	98%
Pravastatin 10	0.0%	0.95	0.19	0.76	19%	33%	58%
Pravastatin 20	0.0%	1.17	0.23	0.94	27%	46%	76%
Pravastatin 40	0.0%	1.38	0.28	1.10	35%	60%	88%
Rosuvastatin 5	0.0%	1.84	0.37	1.47	56%	84%	99%
Rosuvastatin 10	0.3%	2.08	0.42	1.66	66%	91%	100%
Rosuvastatin 20	1.7%	2.32	0.46	1.86	76%	96%	100%
Rosuvastatin 40	1.6%	2.56	0.51	2.05	83%	98%	100%
Simvastatin 10	0.0%	1.31	0.26	1.05	32%	55%	85%
Simvastatin 20	0.1%	1.54	0.31	1.23	42%	69%	94%
Simvastatin 40	0.2%	1.78	0.36	1.42	53%	81%	98%
Simvastatin 80	0.0%	2.01	0.40	1.61	63%	90%	100%

*Elaborated by the authors

Power is calculated assuming a sample size of 800 per arm, 5% type-I error, a standard deviation of LDL change of 0.7 and that non-adherent patients will still reduce their LDL on average 20% of the reduction in adherent patients.

Interpretation of the table: Example of third line (atorvastatin 40): 52.4% of patients in the hospital take atorvastatin 40. Adherent patients are expected to reduce their cholesterol an average of 2.36 mmol/l in the first year, and non-adherent patients are expected to reduce it 0.47 mmol/l. If all patients were on atorvastatin 40, we would have a 77% power to detect a true increase in adherence of 5%, a 97% power to detect a true increase in adherence of 7% and almost a 100% power to detect a true increase in adherence of 10%. Atorvastatin is the most prescribed statin in patients in our study. About the 65% of the sample use.

Recruitment

The pragmatic nature of this trial will allow collaborators to follow different strategies for participant recruitment according to the setting. There are three main approaches for the recruitment of patients who fulfil the inclusion criteria a) in hospital patients at the time of discharge, b) patients attending outpatient clinics, c) and patients who are in the health care facility database and who will be contacted by phone calls and recruited in outpatient clinics.

Assignment of intervention

Randomization: We will use block randomization (varying size), stratifying by centre and with 1:1 allocation between the intervention and control arm. Randomization will be performed centrally using the CommCare platform after eligibility criteria was confirmed, informed consent signed, and baseline information collected. Therefore, the randomized allocation will not be revealed until after a participant was formally entered into the trial. Therefore, concealment of allocation will be complete. The SMS will be automatically generated by the CommCare platform and unknown to the investigators in contact with patients.

Blinding: Because of the nature of the intervention (SMS messages), it is not possible to include blind participants. However, the tx2theart trial will perform a blinded assessment of outcomes. Research personnel collecting data on clinical events, adherence scales, and biomarkers will not have access to treatment allocation. The laboratory results will be performed once trial follow-up is completed.

Data collection methods

Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered in the CommCare platform, designed by Dimagi. CommCare is an open source mobile platform designed for data collection, client management, decision support, and behaviour change communication. The electronic devices (desktop computers, laptops and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by Fundación Cardiovascular de Colombia.

Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while maximizing retention to follow-up. The following strategies to prevent loss to follow-up will be used. 1) One phone call at the third month of participation. Trained personnel different from the other interviewers will phone the participants to guarantee the blind design. Professionals in charge of the follow-up are trained in patient contact with the ability to empathize with volunteers. 2) We will register at least three relatives' numbers to contact in case we are not able to reach the patient, and we will phone the participant's relatives. 3) We will register the addresses of participants in case we cannot reach the patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the participants a contact phone number to let us to know if they change their phone number contact. We will explain these strategies to participants to get permission for further contact.

Clinical outcomes

Death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization will be defined by local investigators based on clinical notes and clear objective criteria using the suggestions provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials[18].

Self-reported adherence

To estimate adherence, we will use a self-reported scale named Medication Adherence Report Scale 5 (MARS-5), which is a valid and reliable scale for measuring adherence to medication in chronic conditions at trial entry and at the final assessment at 12 months[19]. The MARS-5 Scale elicits patients' reports of non-adherence. To diminish the social pressure on patients to report high adherence, items are phrased in a non-threatening manner, and patients are assured that their responses will be anonymous and confidential. Participants are asked to rate the frequency with which they engaged in each of five aspects of non-adherent listed behaviours (e.g., 'I forget to take these medicines', 'I stop taking these medicines for a while') using a 5-point scale ranging from 'never' to 'always'. Scores for each item are summed to give a total score that ranged from 5 to 25, with higher scores indicating higher levels of adherence. Patients will be recruited at least 30 days, after discharge in the case of their first cardiovascular event.. A trained psychologist will administer the MARS-5 during the first interview.

In order to complete information about medications, we will ask patients about prescribed medication.

Biomarkers

Physiological measurements of heart rate and blood pressure will be measured using a calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by trained health care professionals. Patients will sit quietly for 10 minutes before the examinations.

Blood LDL-C: Quantification of serum LDL will be performed using automated equipment by a direct method.

Recent large epidemiological studies confirmed that resting heart rate is an independent predictor of cardiovascular mortality. Heart rate decrease is itself an important mechanism of the benefit of the blockers and other drugs that reduce heart rate after an acute myocardial infarction[(1–4)]. Controversies on the optimal dose to obtain results remain, but the reduction in heart rate is notorious in patients receiving beta-blockers[5]. In Colombia, beta-blockers are a first-line drug used for secondary prevention. The most

frequently beta-blocker is carvedilol, which exhibits advantages in decreasing heart rate and mortality in patients with some type of cardiovascular event[6].

Data management

Data will be stored on a secure system and will be password protected. All trial procedures will be performed in accordance with the principles of Good Clinical Practice (GCP). Essential documents of the sponsor/trial organizers and investigators will be retained for at least 10 years after completion of the trial. The research staff will maintain appropriate medical and research records for this clinical study and meet with the regulatory and institutional frameworks for the protection of the confidentiality requirements. As sponsor of this trial, Fundación Cardiovascular de Colombia will allow regulatory agencies to examine (under applicable law) clinical records to check the quality, safety and progress of the study.

Statistical Analysis

The main analyses will be an "intention to treat", meaning it will compare all patients allocated to the intervention to patients allocated to the control arm, regardless of whether they received the allocated intervention. A sensitivity per protocol analysis will also be performed. For continuous outcomes (including all primary outcomes: LDL cholesterol, blood pressure and Heart rate), we will estimate an ANCOVA model regressing the 12-month difference from baseline in the allocated group and the mean centred baseline values of the continuous variable. Deaths and hospitalizations will be analysed using Cox regression models to estimate hazard ratios. The assumptions underlying all of these models will be assessed. For subgroup analyses, we will only consider a limited number of variables that, given the mechanism of action of the intervention, could modify the effect of the intervention. A detailed statistical analysis plan setting out full details of the proposed analyses will be prepared and completed before the trial database is locked for final analysis. Missing data will be managed by an intention to treat analysis.

Data Monitoring

Data monitoring will be executed according to GCP Guidelines. This trial is a large, pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change behaviour and increase adherence of safe and proven effective interventions for secondary prevention that have been in clinical use for decades. Clinical management for underlying conditions will remain as per hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic)

occurring because of participation in this research study was assessed as low risk to participants in each of these categories. Based on the low risks associated with this trial, there will not be a data monitoring committee. However, a monitoring plan to ensure appropriate performance of the trial will be developed, which will incorporate 100% central monitoring in conjunction with procedures, such as investigator training and meetings and written guidance. All data will be subject to statistical monitoring, and at least 10% of data will be subjected to on-site monitoring. Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for 15 years after the end of the trial.

Patient and Public Involvement

We did not directly include PPI in this study. However, to design the intervention, we interviewed patients about their perceptions of e-health and their previous experience with mobile cellular phone technology and obtained their feedback about the messages in the intervention. The Ethics Committee evaluated and approved our research included patient representatives.

ETHICS AND DISSEMINATION

Protocol amendments

The protocol for the trial has not been modified.

Ethical considerations

The study will be performed in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki.

Ethical approval

The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial.

Informed Consent:

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient will be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. Written consent must be given by the patient

and/or the legal guardian of the patient after detailed information about the study is provided in accordance with any national provisions on the protection of clinical study patients. The verbal explanation will cover all of the elements specified in the written information provided to the patient. Patients and/or legal guardians will be required to sign and date the informed consent form. Patients who refuse to give or who withdraw written informed consent will not be included or continue in the study. The trial will include a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or law of protection of personal data, where the study team is authorized to handle personal and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be recorded and stored for a set time. Eligible participants will only be included in the study after signing “Txt2Heart-Colombia” informed consent (testified, where required by law or regulation), as approved by the ethics committees. The process will be documented in the patient source documents, specifically in CRFs (Case Report Form).

Confidentiality: Information about the study subjects will be kept confidential. The investigators will ensure the anonymity of patients, and patients will not be identified by name in any document. Informed consent forms and patient recruitment registration will be kept strictly confidential only to permit identification of the patient at Fundación Cardiovascular de Colombia. Information about the study subjects will be handled under the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law of data protection). The regulations that require an authorization signed by the patient including the follow information: What protected health information (PHI) will be collected from the study subjects, who will have access to that information and why, who will use and disclose that information and the right to withdraw his/her authorization to use their PHI.

Access to data

The principal investigator and sub-investigators will have access to the data to verify and analyse the results. To ensure confidentiality, all of the investigators will be blinded of participant identification.

Ancillary and post-trial care

Due to its low risk, the intervention in this trial will not include insurance for participants. However, we will refer patients to their medical services in case we think that they need assistance. Furthermore, a full explanation of the scope and limitations of the study will be told to the patients before they sign the informed consent.

Dissemination policy

The Txt2heart Colombia trial is aimed to provide high level evidence that evaluates whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the health local authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

The results from the trial will be published in an open journal to provide scientists, clinicians and policymakers access to the data.

REFERENCES

1. Perel, P., et al., *Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease.* Glob Heart, 2015. **10**(2): p. 99-110.
2. Perel, P., et al., *Noncommunicable diseases and injuries in Latin America and the Caribbean: time for action.* PLoS Med, 2006. **3**(9): p. e344.
3. World Health Organization. *Model List of Essential Medicines (20th List)*. 2017 [cited [Accessed June 23 2017]; Available from: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.
4. Yusuf, S., *Two decades of progress in preventing vascular disease.* Lancet, 2002. **360**(9326): p. 2-3.
5. Yusuf, S., et al., *Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey.* Lancet, 2011. **378**(9798): p. 1231-43.
6. Rashid, M.A., et al., *Medication taking in coronary artery disease: a systematic review and qualitative synthesis.* Ann Fam Med, 2014. **12**(3): p. 224-32.
7. R.M., *Patient factors that influence cardiovascular medication adherence (MSc Thesis)*. 2014, London School of Hygiene & Tropical Medicine.
8. Santo, K., et al., *Interventions to improve medication adherence in coronary disease patients: A systematic review and meta-analysis of randomised controlled trials.* Eur J Prev Cardiol, 2016. **23**(10): p. 1065-76.
9. International Telecommunications Union. *ICT Facts and figures*. 2014 [cited [Accessed July 20, 2017]; Available from: http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2014-e.pdf.
10. Free, C., et al., *The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review.* PLoS Med, 2013. **10**(1): p. e1001362.
11. Catalani, C., et al., *mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature.* Open AIDS J, 2013. **7**: p. 17-41.

12. Adler, A.J., et al., *Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2017. **4**: p. Cd011851.
13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Abroms, L.C., et al., *Developing and Pretesting a Text Messaging Program for Health Behavior Change: Recommended Steps.* JMIR Mhealth Uhealth, 2015. **3**(4): p. e107.
15. Michie, S., et al., *The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions.* Ann Behav Med, 2013. **46**(1): p. 81-95.
16. Moore, G.F., et al., *Process evaluation of complex interventions: Medical Research Council guidance.* BMJ, 2015. **350**: p. h1258.
17. Uribe-Rodríguez, A., et al., *Designing a text messaging program to increase adherence to medication for the secondary prevention of cardiovascular disease.* medRxiv **19002683**; doi: https://doi.org/10.1101/19002683
18. Hicks, K.A., et al., *2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards).* Circulation, 2015. **132**(4): p. 302-61.
19. Mahler, C., et al., *Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany.* J Eval Clin Pract, 2010. **16**(3): p. 574-9.

Authors' contributions

Study director

Norma Cecilia Serrano Díaz, MSc: Senior researcher and Research Department Director at Fundación Cardiovascular de Colombia. Dr Serrano participated in choosing of the biomarkers and the processing design for the biological samples.

Principal investigator

Anderson Bermon, MD, MSc: associate researcher and epidemiologist at Fundación Cardiovascular de Colombia, Demography and Biostatistics PhD student at CES University. Dr. Bermon participated in the trial design and studied the impact of the results in Colombia, considering the healthcare system limitations.

Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor Faculty of Psychology, Pontificia Bolivariana University. Dr. Uribe designed the message

intervention and studied the behavioural theories that support the intervention methodology.

Study chair

Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University College London at Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas conceived the idea of conducting the trial and participated in the methodology design of the trial.

Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived the idea of conducting the trial and participated in the methodology design of the trial.

Sub-investigators:

Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research Department of Primary Care and Population Health, University College London. Dr. Murray contributed in the intervention design and message validity process.

David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the statistical analysis and data management of the trial.

Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and participated in the validity process of the message intervention.

Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins contributed in the message intervention design.

Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of Pharmacy, University College London. Dr. Horne participated in the validity process of the message intervention and choosing adherence scales.

Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the processing design for biological samples.

Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.

Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez participated in the intervention design.

Acknowledgments statement

We thank the Cardiology Department medical staff at Fundación Cardiovascular de Colombia for their help with developing our research questions.

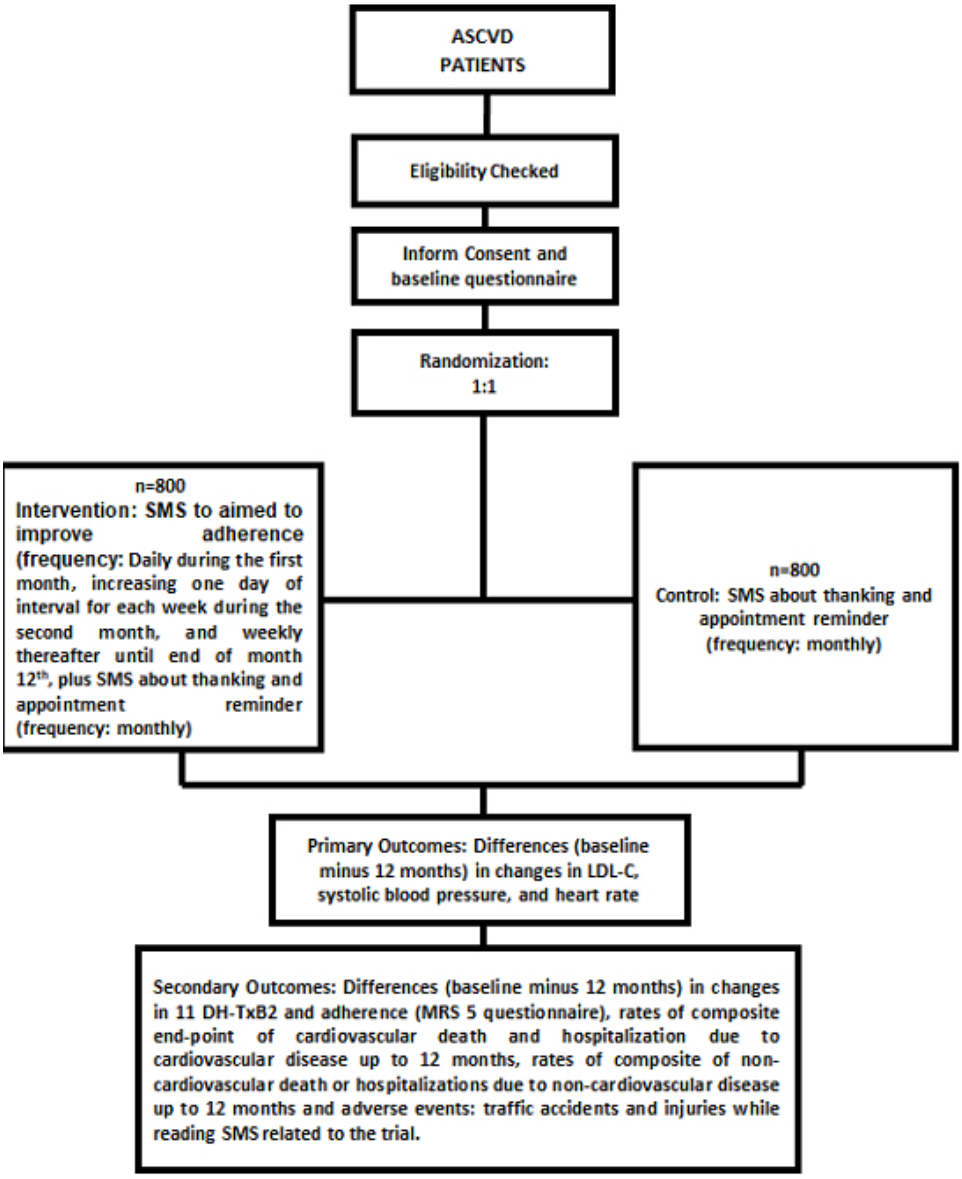
Funding statement

This work was supported by COLCIENCIAS code 656672553352 grant 899-2015

Fundación Cardiovascular de Colombia, Floridablanca
London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded Reference MR/N021304/1
Universidad Pontificia Bolivariana, Bucaramanga sectional

Competing interests' statement

All authors declare there is not conflict of interest.
All funding institutions declare there is not conflict of interest.


ASCVD PATIENTS
Eligibility Checked
Inform Consent and baseline questionnaire
Randomization: 1:1
n=800
Intervention: SMS to aimed to improve adherence (frequency: Daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th, plus SMS about thanking and appointment reminder (frequency: monthly)
n=800
Control: SMS about thanking and appointment reminder (frequency: monthly)
Primary Outcomes: Differences (baseline minus 12 months) in changes in LDL-C, systolic blood pressure, and heart rate
Secondary Outcomes: Differences (baseline minus 12 months) in changes in 11 DH-TxB2 and adherence (MRS 5 questionnaire), rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months, rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months and adverse events: traffic accidents and injuries while reading SMS related to the trial.

Flowchart

Supplementary file

Trial Summary

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT03098186
Date of registration in primary registry	March 10, 2017
Source(s) of monetary or material support	Departamento Administrativo de Ciencia, Tecnología e Innovación Colombia COLCIENCIAS Fundación Cardiovascular de Colombia London School of Hygiene and Tropical Medicine University College, London Universidad Pontificia Bolivariana
Primary sponsor	COLCIENCIAS Contact: contacto@colciencias.gov.co (+57) (1) 6258480 ext. 2081
Secondary sponsor (s)	Fundación Cardiovascular de Colombia
Contact for public queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Contact for scientific queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Public title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol
Scientific title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Countries of recruitment	Colombia
Health condition(s) or problem(s) studied	Acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation) Stable angina Ischemic cerebrovascular disease Peripheral arterial disease
Interventions	Active treatment: will consist of SMS that are aimed to modified behavioural factors associated with poor adherence to cardiovascular medications used in secondary prevention. The SMS will be delivered daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th. In addition, they will receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly. Control: participants will only receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly.
Key inclusion and exclusion criteria	Inclusion Criteria: Age ≥18 years old Sexes eligible for study: both History of at least one of the following arterial occlusive events: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Own at least one mobile phone

	Ability to read and understand text messages (SMS) Intention to stay in the country of recruitment during the next 12 months Exclusion Criteria: Contraindication to take all cardiovascular medications used in secondary prevention. Participation in another randomized clinical trial that could interfere with adherence to treatment.
Study type	Two-parallel arm, only-blind, individually randomized controlled trial.
Date of first enrolment	April 2017
Target sample size	1600
Recruitment status	Recruiting
Primary outcome(s)	Differences in changes (baseline minus 12 months) of: Low density lipoprotein cholesterol (LDL-C) Systolic Blood pressure Heart Rate
Key secondary outcomes	Differences in the changes (baseline minus 12-months) of: (i) Adherence to cardiovascular medications used in secondary prevention measured by MARS-5 questionnaire; and (ii) Urinary levels of 11 dh-TxB2. Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months. Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months Adverse events: traffic accidents and injuries while reading SMS related to the trial.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#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	18
Roles and responsibilities: committees	#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)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies	5

		(published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	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, non-inferiority, exploratory)	7
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	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)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	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)	9
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	11

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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	12
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	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	13

		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	
Data collection plan: retention	#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	13
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	14
Statistics: outcomes	#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	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#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)	14
Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15

formal committee		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	
Data monitoring: interim analysis	#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	15
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
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)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
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	16
Dissemination policy: trial results	#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	17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	17

reproducible research		participant-level dataset, and statistical code	
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16
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	13

BMJ Open

Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028017.R3
Article Type:	Protocol
Date Submitted by the Author:	30-Oct-2019
Complete List of Authors:	Bermon Angarita, Anderson; Fundacion Cardiovascular de Colombia, Research; CES University Uribe Rodríguez, Ana; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Pérez-Rivero, Paula; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Prieto-Merino, David; London School of Hygiene & Tropical Medicine Cáceres Rivera, Diana ; Universidad Cooperativa de Colombia, Nursing Guio, Elizabeth; Fundacion Cardiovascular de Colombia, Metabolism and Genoma Laboratory Atkins, Louise; University College London Research Department of Epidemiology and Public Health Horne, Robert; University College London Murray, Elizabeth; University College London, Primary Care and Population Health Serrano Díaz, Norma; Fundación Cardiovascular de Colombia, Direction of research Free, Caroline; London School of Hygiene and Tropical Medicine, Public Health interventions Unit Perel, Pablo; LSHTM, EPH Casas, Juan Pablo ; University College London Medical School, Clinical Epidemiology and Informatics ; Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Research
Primary Subject Heading:	Public health
Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: The Txt2heart-Colombia randomized controlled trial protocol

Anderson Bermon*
Fundación Cardiovascular de Colombia
Research department
Av. 5 # 6-33, Floridablanca, Santander, Colombia.
Postal code: 681004
Telephone number: (+57) 3002053041
FAX: (+57) 6796470
andersonbermon@fcv.org
*Corresponding author

Ana Fernanda Uribe Rodríguez
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

Paula Fernanda Pérez-Rivero
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

David Prieto-Merino
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine
London, UK

Diana Isabel Cáceres Rivera
Cooperativa Colombia University
Faculty of Nursing
Bucaramanga, Santander, Colombia

Elizabeth Guio
Metabolism and Genome Laboratory
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Lou Atkins
Faculty of Health Psychology
University College London
London, UK.

Robert Horne
Centre for Behavioural Medicine
UCL School of Pharmacy
University College London
London, UK.

Elizabeth Murray
Research Department of Primary Care and Population Health
University College London

London, UK.

Norma Cecilia Serrano Díaz
Research Department
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Caroline Free
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Pablo A. Perel
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Juan P. Casas
Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
VA Boston Healthcare System
Boston, Massachusetts, USA.

Keywords: Cardiovascular diseases, Health behavior, Medications adherence, mHealth, text messaging

Word count: 5006

Abstract

Introduction: Anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that adherence to these cardiovascular medications is far from ideal. A recent Cochrane review showed a potential beneficial effect of SMS interventions on adherence to medication in ASCVD patients.

Methods and analysis: The Txt2heart study is a pragmatic randomized single-blind controlled trial. The objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobile phones to improve adherence to cardiovascular medications in patients with ASCVD. The intervention consists of behavioural techniques delivered via SMS. The primary outcome is change in blood serum low-density lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins. Secondary outcomes will include systolic blood pressure as an indicator of adherence to blood-lowering therapies and heart rate as an indicator of adherence to beta-blockers, urine levels of **11**-dehydrothromboxane B2 (11dhTxB2), self-reported adherence to cardiovascular medications and rates of cardiovascular death or hospitalization due to cardiovascular disease.

Ethics and dissemination: The study will be performed in compliance with the protocol, regulatory requirements, Good Clinical Practice and ethical principles of the Declaration of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to

evaluate whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the local health authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

Trial registration number: ClinicalTrials.gov: NCT03098186

Strengths and limitations of this study.

The trial uses an innovative intervention through SMS methodology based on behaviour theories.

The trial uses biomarkers to evaluate medication adherence.

The trial is the largest evaluating SMS to increase adherence for cardiovascular secondary prevention

Measuring adherence is challenging; we are triangulating data from biomarkers and self-reported adherence to improve the accuracy of the trial measure of effect

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death worldwide. Approximately 35 million people worldwide have an acute coronary event or cerebrovascular event annually, and one quarter of these events occur in people with established ASCVD[1]. These arterial occlusive events occur at an early age in low and middle-income countries (LMICs), which affects economically active populations and results in large economic impacts[2].

Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the risk of ASCVD events in patients with established ASCVD, and these agents are included in the list of the World Health Organization (WHO) Essential Medicines List (EML)[3]. Treatment with these four proven medications (together with smoking cessation) prevents or postpones approximately 75-80% of recurrent vascular events and their complications, such as death and disability[4].

Unfortunately, there is abundant evidence that the worldwide adherence to these cardiovascular medications in patients with ASCVD is far from ideal. Less than half of patients with known ASCVD disease in high-income countries are receiving this group of cardiovascular medications, and the situation is much worse in LMICs. The PURE

study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types of cardiovascular drugs[5].

A wide range of socio-economic and service level factors influence whether patients obtain medications, including the availability of medication (drugs out of stock), the lack of affordable medication and service factors, such as the availability and training of health care providers. Adherence to medication focuses on whether patients take the prescribed medication. Two recent systematic reviews on patient factors that affect adherence to ASCVD medications in secondary prevention showed that these factors go far beyond simply "forgetting" to take the medication and include a range of factors, including patients' perceptions of the cause and prognosis of the illness (e.g., fatalistic perceptions or absence of symptoms) and/or the risks and benefits of medications (e.g., fear of side effects or concern about multiple medications), the patient-physician relationship, availability of family/social network support, and comorbidities (e.g., depression)[6 7].

A recent systematic review from RCTs on interventions to improve adherence to medications in patients with ASCVD demonstrated several potential interventions, and importantly, simple interventions may be as effective as complex ones (and therefore easier to replicate)[8]. However, this review also highlighted many limitations in the current evidence, such as risk of bias, small sample sizes and lack of studies in LMICs, where most of the patients with ASCVD live. Among the most promising simple strategies to increase adherence, this review singled out Short Message Service (SMS) interventions.

Mobile phones have become an "essential" instrument of daily life worldwide, with approximately 7 billion subscribers, of whom 78% are based in LMICs[9]. This use makes mobile phones an "ideal instrument" to deliver health behaviour change interventions to large numbers of people at a low cost. Systematic reviews of RCTs using mHealth interventions confirm that SMS can be successful in changing behaviour, including smoking cessation and improved adherence to HIV medications[1011]. Patient factors influencing adherence, such as knowledge attitudes and beliefs, could be amenable to change using mobile phone messages sent to patients.

A recent Cochrane review evaluated the effects of SMS on adherence to medications in patients with ASCVD[12]. The review identified seven trials (1310 participants) and showed a beneficial effect of SMS on adherence to medications in six of these trials. However, the quality of the evidence was very low. The Cochrane review identified the following limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV) most studies recruited only patients with acute coronary syndrome, which

leaves out an important group of patients with other arterial occlusive events (e.g., ischaemic stroke, peripheral vascular disease and programmed coronary revascularizations) who should be amenable for this type of intervention; (V) few studies were performed in LMICs; and (VI) most trials did not describe the processes behind the SMS content generation, and the few trials that did report these processes did not target the key knowledge and attitudinal factors that are known to influence adherence to medication; instead the interventions were simple "reminders".

In conclusion, given the high prevalence of people with ASCVD in LMICs and the low use of cost-effective secondary prevention medications, a low-cost intervention that builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to improve public health. The current evidence shows that SMS interventions based on behaviour-change techniques are a potentially effective strategy to increase adherence to medications in people with ASCVD. However, further large trials are needed.

To provide the high-quality evidence needed to assess the effect of SMS interventions based on behaviour-change techniques to increase adherence to medications in patients with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the efficacy and safety of SMS on adherence to cardiovascular medications. The trial is being performed in a setting (Colombia) where patient factors, such as knowledge, attitudes and beliefs, are important determinants of adherence. In this context, medicines are widely available and generally affordable, so an intervention delivered to patients via SMS has the potential to be effective.

METHODS AND ANALYSIS

This protocol is reported following the SPIRIT Standard Protocol Items recommendations for Interventional Trials[13] (see supplementary file 1).

Aim and objectives

The primary objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobiles phones to improve adherence to cardiovascular medications in patients with atherosclerotic cardiovascular disease (ASCVD). We will assess the intervention efficacy via the measurement of blood serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as

an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart rate as an indicator of adherence to beta-blockers.

The secondary objective is to assess the impact of mobile text messaging on self-reported adherence to medications, hospitalizations, and the composite end-point of incident Major Adverse Cardiovascular Events (MACE) at 12 months.

Choice of comparator

The trial design is a two-parallel arm in which the comparator is a control follow up. Patients allocated to the control group will receive monthly messages that convey the gratitude of the research team for their participation and emphasize the importance of follow up. The choice of comparator was guided by considerations of enhancing acceptability of the trial and enhancing retention and follow-up rates, while not materially altering medication-taking behaviours or causing participants harm or discomfort. Participants will be told that they could be allocated to one of two different groups. Furthermore, our intervention will not interfere with medical treatment. Patients will be warned that the study does not replace medical assistance and that they must continue with their traditional treatment.

Trial design

Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled trial. This design is aimed to minimize any potential bias that affects the internal validity of the study. The selection criteria were designed to increase the number of potential beneficiaries of the intervention and to keep the selection process as close as possible to the future scenario in which the intervention will be implemented. Therefore, Txt2THeart-Colombia is pragmatic in design. The active intervention will be the SMS delivered to mobile phones, and the content of the SMS is aimed to modify behaviours associated with poor adherence to ASCVD medications in ASCVD patients. Randomization will be performed as block randomization with a 1:1 allocation.

Study setting

We will recruit patients at Fundación Cardiovascular in Colombia, which has a staff that is knowledgeable in trials and a sufficient pool of eligible patients. The trial will continue to add sites, if necessary, to ensure that the sample size is achieved. There is no limit to the maximum number of patients to be recruited in each site.

Eligibility criteria

Inclusion criteria: Adult patients ≥18 years old with a history of at least one of the following arterial occlusive events will be included: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischaemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Patients should own a mobile phone and be able to read SMS.
Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular secondary prevention medications.

Intervention

The intervention under evaluation consists of *behavioural change techniques* (BCTs) delivered via SMS. We developed our intervention following the recommendations of Abroms et al[14]. First, we reviewed the literature on individual level factors that influence adherence to medication. We performed country-specific qualitative studies using focus group discussions and semi-structured interviews to evaluate cardiovascular patients' perceptions about mHealth programmes to determine the necessary content and preferred timing and frequency of the SMS messages. To construct the content of the SMS, we wrote messages using educational and enabling behaviour change functions and established BCTs to target the potentially modifiable factors that influence the adherence referred to in the literature and found in our qualitative studies[15]. Finally, we tested the SMS messages with participants and adapted the messages based on their feedback to ensure the messages were understandable, acceptable, and relevant[16]. The resultant intervention delivered by SMS provides information about health consequences of adherence or non-adherence, instruction on how to take medication, medicine-taking prompts and cues, support in establishing medicine-taking habits, reframing medicine-taking and provides or encourages social support for taking medication[17]. The messages were designed according to the Transtheoretical Model (TTM) (Prochaska & DiClemente, 1992) and were aimed to enhance actions related to the steps and processes of this model. We will send messages daily the first month, three times per week the second month and once weekly the last ten months. This reducing frequency is consistent with the TTM, which suggests that people in the early stages of change require more intense input than people in later stages. In accordance with data from the focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The intervention will be delivered through an electronic platform, and it will be a one-way intervention. We will explain patients that they should not answer the messages, but they will be able to request to stop receiving the messages and withdraw from the trial by sending a message with the word "STOP". We will explain to patients that they should

send the 'stop' message in this situation. Stop messages will be saved and monitored by a trained engineer, separate from the study team, in order to maintain blinding. Similarly, a trained engineer, separate from the study team, will save and monitor the patients' answers if they respond to the messages. Because of the pragmatic nature of our study we will not tailor the messages. The trial intervention will start the day after recruitment and continue for 12 months or until the participant withdraws from the study or dies. The follow-up duration will be at least 12 months to a maximum of 36 months. Participants will not receive messages after month 12.

Outcomes

The primary outcome was selected for its clinical relevance and include: differences in changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of adherence to statins.

The following secondary outcomes will be included: *systolic blood pressure* as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs), *heart rate* as an indicator of adherence to beta-blockers*, urine levels of 11 dhTxB2* as an indicator of adherence to antiplatelet therapy; *self-reported adherence to cardiovascular medications* used in secondary prevention as measured using the MARS-5 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular disease and non-cardiovascular death or hospitalizations due to non-cardiovascular disease. We will also include road traffic crashes (the only potential known hazard of text messaging) and death due to all causes as secondary outcomes.

Participant timeline

Participants who fulfil the eligibility criteria and provide their informed consent will be recruited into the txt2heart trial. After the participant provided informed consent, baseline characteristics will be collected at the first visit using questionnaires (MARS-5 and PHQ-9 Patient Health Questionnaire), blood samples, blood pressure, and heart rate. Participants will be randomized to the intervention or control arm. The trial intervention will start the day after recruitment and will continue for 12 months to a maximum of 36 months, or when the participant withdraws from the study, or dies. We will perform a phone follow-up interview three months later, during the second visit, to evaluate adequate SMS delivery and the occurrence of clinical events. Finally, we will collect data on self-reported adherence to cardiovascular medications (MARS-5), blood pressure, heart rate and clinical end-points in the third visit (12 months later). The 12-month follow up marks the primary outcome point. For patients with follow up beyond 12 months, we

will perform (by phone) assessments of clinical outcomes (death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization) every 6 months until 36 months, the longest available follow-up (figure 1).

Figure 1.

Trial flowchart

Sample Size

The sample size of the study is 1600 participants. The power of the study was calculated for differences between arms in the reduction in the primary outcome LDL-C (12-month minus baseline).

The power of the study was calculated for the primary outcome of the clinical trial, i.e., differences in the levels of physiological markers of adherence to cardiovascular drugs. Because the power of a sample size depends on several parameters in this study, such as the doses are finally prescribed to patients and what proportion of patients will adhere, we performed several power and sample size calculations for different scenarios. We concluded that 1600 was a reasonable sample size. For example, assuming that adherent patients to 40 mg atorvastatin for 12 months are expected to have an average LDL-cholesterol reduction of 91.3 mg/dL (data derived from randomized clinical trials), and non-adherent patients will reduce LDL-cholesterol by an average of 18.3 mg/dL (or 20% of the reduction in adherent patients) and that the standard deviation of the changes is approximately 27.07 ml/dL, we would have 97% power to detect a 7% difference in adherence between arms or a 77% power to detect a 5% difference (always using a 5% type-I error). However, if patients were on 20 mg atorvastatin and the expected reductions in LDL-C were 80.05 mg/dL in adherent and 16.01 mg/dL in non-adherent patients, then we would have a 91% power to detect a 7% difference of adherence between arms and a 66% power to detect a 5% difference between arms (table 1).

Table 1

Sample size calculations

Statins and its frequency in trials		Reduction in LDL after a year of treatment in adherents and non-adherents			Power to detect differences depending on adherence increase		
	%	**AD=yes**	**AD=No**	**Dif**	**5.0%**	**7.0%**	**10.0%**
Atorvastatin 10	1.5%	1.79	0.36	1.43	53%	82%	98%

Atorvastatin 20	32.9%	2.07	0.41	1.66	66%	91%	100%
Atorvastatin 40	52.4%	2.36	0.47	1.89	77%	97%	100%
Atorvastatin 80	9.4%	2.64	0.53	2.11	85%	99%	100%
Fluvastatin 20 mg	0.0%	1.02	0.20	0.82	21%	37%	64%
Lovastatin 40	0.0%	1.77	0.35	1.42	53%	81%	98%
Pravastatin 10	0.0%	0.95	0.19	0.76	19%	33%	58%
Pravastatin 20	0.0%	1.17	0.23	0.94	27%	46%	76%
Pravastatin 40	0.0%	1.38	0.28	1.10	35%	60%	88%
Rosuvastatin 5	0.0%	1.84	0.37	1.47	56%	84%	99%
Rosuvastatin 10	0.3%	2.08	0.42	1.66	66%	91%	100%
Rosuvastatin 20	1.7%	2.32	0.46	1.86	76%	96%	100%
Rosuvastatin 40	1.6%	2.56	0.51	2.05	83%	98%	100%
Simvastatin 10	0.0%	1.31	0.26	1.05	32%	55%	85%
Simvastatin 20	0.1%	1.54	0.31	1.23	42%	69%	94%
Simvastatin 40	0.2%	1.78	0.36	1.42	53%	81%	98%
Simvastatin 80	0.0%	2.01	0.40	1.61	63%	90%	100%

*Elaborated by the authors

Power is calculated assuming a sample size of 800 per arm, 5% type-I error, a standard deviation of LDL change of 0.7 and that non-adherent patients will still reduce their LDL on average 20% of the reduction in adherent patients.

Interpretation of the table: Example of third line (atorvastatin 40): 52.4% of patients in the hospital take atorvastatin 40. Adherent patients are expected to reduce their cholesterol an average of 2.36 mmol/l in the first year, and non-adherent patients are expected to reduce it 0.47 mmol/l. If all patients were on atorvastatin 40, we would have a 77% power to detect a true increase in adherence of 5%, a 97% power to detect a true increase in adherence of 7% and almost a 100% power to detect a true increase in adherence of 10%. Atorvastatin is the most prescribed statin in patients in our study. About the 65% of the sample use.

Recruitment

The pragmatic nature of this trial will allow collaborators to follow different strategies for participant recruitment according to the setting. There are three main approaches for the recruitment of patients who fulfil the inclusion criteria a) in hospital patients at the time of discharge, b) patients attending outpatient clinics, c) and patients who are in the health care facility database and who will be contacted by phone calls and recruited in outpatient clinics.

Assignment of intervention

Randomization: We will use block randomization (varying size), stratifying by centre and with 1:1 allocation between the intervention and control arm. Randomization will be performed centrally using the CommCare platform after eligibility criteria was confirmed, informed consent signed, and baseline information collected. Therefore, the randomized allocation will not be revealed until after a participant was formally entered into the trial. Therefore, concealment of allocation will be complete. The SMS will be automatically generated by the CommCare platform and unknown to the investigators in contact with patients.

Blinding: Because of the nature of the intervention (SMS messages), it is not possible to include blind participants. However, the tx2theart trial will perform a blinded assessment of outcomes. Research personnel collecting data on clinical events, adherence scales, and biomarkers will not have access to treatment allocation. The laboratory results will be performed once trial follow-up is completed.

Data collection methods

Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered in the CommCare platform, designed by Dimagi. CommCare is an open source mobile platform designed for data collection, client management, decision support, and behaviour change communication. The electronic devices (desktop computers, laptops and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by Fundación Cardiovascular de Colombia.

Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while maximizing retention to follow-up. The following strategies to prevent loss to follow-up will be used. 1) One phone call at the third month of participation. Trained personnel different from the other interviewers will phone the participants to guarantee the blind design. Professionals in charge of the follow-up are trained in patient contact with the ability to empathize with volunteers. 2) We will register at least three relatives' numbers to contact in case we are not able to reach the patient, and we will phone the participant's relatives. 3) We will register the addresses of participants in case we cannot reach the patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the participants a contact phone number to let us to know if they change their phone number contact. We will explain these strategies to participants to get permission for further contact.

Clinical outcomes

Death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization will be defined by local investigators based on clinical notes and clear objective criteria using the suggestions provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials[18].

Self-reported adherence

To estimate adherence, we will use a self-reported scale named Medication Adherence Report Scale 5 (MARS-5), which is a valid and reliable scale for measuring adherence to medication in chronic conditions at trial entry and at the final assessment at 12 months[19]. The MARS-5 Scale elicits patients' reports of non-adherence. To diminish the social pressure on patients to report high adherence, items are phrased in a non-threatening manner, and patients are assured that their responses will be anonymous and confidential. Participants are asked to rate the frequency with which they engaged in each of five aspects of non-adherent listed behaviours (e.g., 'I forget to take these medicines', 'I stop taking these medicines for a while') using a 5-point scale ranging from 'never' to 'always'. Scores for each item are summed to give a total score that ranged from 5 to 25, with higher scores indicating higher levels of adherence. Patients will be recruited at least 30 days, after discharge in the case of their first cardiovascular event.. A trained psychologist will administer the MARS-5 during the first interview.

In order to complete information about medications, we will ask patients about prescribed medication.

Biomarkers

Physiological measurements of heart rate and blood pressure will be measured using a calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by trained health care professionals. Patients will sit quietly for 10 minutes before the examinations.

Blood LDL-C: Quantification of serum LDL will be performed using automated equipment by a direct method.

Recent large epidemiological studies confirmed that resting heart rate is an independent predictor of cardiovascular mortality. Heart rate decrease is itself an important mechanism of the benefit of the blockers and other drugs that reduce heart rate after an acute myocardial infarction[(1–4)]. Controversies on the optimal dose to obtain results remain, but the reduction in heart rate is notorious in patients receiving beta-blockers[5]. In Colombia, beta-blockers are a first-line drug used for secondary prevention. The most

frequently beta-blocker is carvedilol, which exhibits advantages in decreasing heart rate and mortality in patients with some type of cardiovascular event[6].

Data management

Data will be stored on a secure system and will be password protected. All trial procedures will be performed in accordance with the principles of Good Clinical Practice (GCP). Essential documents of the sponsor/trial organizers and investigators will be retained for at least 10 years after completion of the trial. The research staff will maintain appropriate medical and research records for this clinical study and meet with the regulatory and institutional frameworks for the protection of the confidentiality requirements. As sponsor of this trial, Fundación Cardiovascular de Colombia will allow regulatory agencies to examine (under applicable law) clinical records to check the quality, safety and progress of the study.

Statistical Analysis

The main analyses will be an "intention to treat", meaning it will compare all patients allocated to the intervention to patients allocated to the control arm, regardless of whether they received the allocated intervention. A sensitivity per protocol analysis will also be performed. For continuous outcomes (including: LDL cholesterol, blood pressure and Heart rate), we will estimate an ANCOVA model regressing the 12-month difference from baseline in the allocated group and the mean centred baseline values of the continuous variable. Deaths and hospitalizations will be analysed using Cox regression models to estimate hazard ratios. The assumptions underlying all of these models will be assessed. For subgroup analyses, we will only consider a limited number of variables that, given the mechanism of action of the intervention, could modify the effect of the intervention. A detailed statistical analysis plan setting out full details of the proposed analyses will be prepared and completed before the trial database is locked for final analysis. Missing data will be managed by an intention to treat analysis.

Data Monitoring

Data monitoring will be executed according to GCP Guidelines. This trial is a large, pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change behaviour and increase adherence of safe and proven effective interventions for secondary prevention that have been in clinical use for decades. Clinical management for underlying conditions will remain as per hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring because of participation in this research study was assessed as low risk to

participants in each of these categories. Based on the low risks associated with this trial, there will not be a data monitoring committee. However, a monitoring plan to ensure appropriate performance of the trial will be developed, which will incorporate 100% central monitoring in conjunction with procedures, such as investigator training and meetings and written guidance. All data will be subject to statistical monitoring, and at least 10% of data will be subjected to on-site monitoring. Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for 15 years after the end of the trial.

Patient and Public Involvement

We did not directly include PPI in this study. However, to design the intervention, we interviewed patients about their perceptions of e-health and their previous experience with mobile cellular phone technology and obtained their feedback about the messages in the intervention. The Ethics Committee evaluated and approved our research included patient representatives.

ETHICS AND DISSEMINATION

Protocol amendments

The protocol for the trial has not been modified.

Ethical considerations

The study will be performed in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki.

Ethical approval

The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial.

Informed Consent:

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient will be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. Written consent must be given by the patient and/or the legal guardian of the patient after detailed information about the study is

provided in accordance with any national provisions on the protection of clinical study patients. The verbal explanation will cover all of the elements specified in the written information provided to the patient. Patients and/or legal guardians will be required to sign and date the informed consent form. Patients who refuse to give or who withdraw written informed consent will not be included or continue in the study. The trial will include a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or law of protection of personal data, where the study team is authorized to handle personal and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be recorded and stored for a set time. Eligible participants will only be included in the study after signing “Txt2Heart-Colombia” informed consent (testified, where required by law or regulation), as approved by the ethics committees. The process will be documented in the patient source documents, specifically in CRFs (Case Report Form).

Confidentiality: Information about the study subjects will be kept confidential. The investigators will ensure the anonymity of patients, and patients will not be identified by name in any document. Informed consent forms and patient recruitment registration will be kept strictly confidential only to permit identification of the patient at Fundación Cardiovascular de Colombia. Information about the study subjects will be handled under the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law of data protection). The regulations that require an authorization signed by the patient including the follow information: What protected health information (PHI) will be collected from the study subjects, who will have access to that information and why, who will use and disclose that information and the right to withdraw his/her authorization to use their PHI.

Access to data

The principal investigator and sub-investigators will have access to the data to verify and analyse the results. To ensure confidentiality, all of the investigators will be blinded of participant identification.

Ancillary and post-trial care

Due to its low risk, the intervention in this trial will not include insurance for participants. However, we will refer patients to their medical services in case we think that they need assistance. Furthermore, a full explanation of the scope and limitations of the study will be told to the patients before they sign the informed consent.

Dissemination policy

The Txt2heart Colombia trial is aimed to provide high level evidence that evaluates whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the health local authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

The results from the trial will be published in an open journal to provide scientists, clinicians and policymakers access to the data.

Limitations

Because, it is probably that most of patients will start the study already on statins, the LDL changes need to be evaluated with caution considering participants' start point. Likewise, power calculation is based on pre versus post statin treatment, rather than on-therapy at baseline changes. Regarding heart rate and blood pressure, because there is not power calculation; comparing entry and exit measures is limited. Finally, adherence measures are limited because we will not establish a baseline and we must consider self-reported scales downsides.

REFERENCES

1. Perel, P., et al., *Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease.* Glob Heart, 2015. **10**(2): p. 99-110.
2. Perel, P., et al., *Noncommunicable diseases and injuries in Latin America and the Caribbean: time for action.* PLoS Med, 2006. **3**(9): p. e344.
3. World Health Organization. *Model List of Essential Medicines (20th List)*. 2017 [cited [Accessed June 23 2017]; Available from: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.
4. Yusuf, S., *Two decades of progress in preventing vascular disease.* Lancet, 2002. **360**(9326): p. 2-3.
5. Yusuf, S., et al., *Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey.* Lancet, 2011. **378**(9798): p. 1231-43.
6. Rashid, M.A., et al., *Medication taking in coronary artery disease: a systematic review and qualitative synthesis.* Ann Fam Med, 2014. **12**(3): p. 224-32.
7. R.M., *Patient factors that influence cardiovascular medication adherence (MSc Thesis)*. 2014, London School of Hygiene & Tropical Medicine.

8. Santo, K., et al., *Interventions to improve medication adherence in coronary disease patients: A systematic review and meta-analysis of randomised controlled trials.* Eur J Prev Cardiol, 2016. **23**(10): p. 1065-76.
9. International Telecommunications Union. *ICT Facts and figures*. 2014 [cited [Accessed July 20, 2017]; Available from: http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2014-e.pdf.
10. Free, C., et al., *The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review.* PLoS Med, 2013. **10**(1): p. e1001362.
11. Catalani, C., et al., *mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature.* Open AIDS J, 2013. **7**: p. 17-41.
12. Adler, A.J., et al., *Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2017. **4**: p. Cd011851.
13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Abroms, L.C., et al., *Developing and Pretesting a Text Messaging Program for Health Behavior Change: Recommended Steps.* JMIR Mhealth Uhealth, 2015. **3**(4): p. e107.
15. Michie, S., et al., *The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions.* Ann Behav Med, 2013. **46**(1): p. 81-95.
16. Moore, G.F., et al., *Process evaluation of complex interventions: Medical Research Council guidance.* BMJ, 2015. **350**: p. h1258.
17. Uribe-Rodríguez, A., et al., *Designing a text messaging program to increase adherence to medication for the secondary prevention of cardiovascular disease.* medRxiv **19002683**; doi: https://doi.org/10.1101/19002683
18. Hicks, K.A., et al., *2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards).* Circulation, 2015. **132**(4): p. 302-61.
19. Mahler, C., et al., *Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany.* J Eval Clin Pract, 2010. **16**(3): p. 574-9.

Authors' contributions

Study director

Norma Cecilia Serrano Díaz, MSc: Senior researcher and Research Department Director at Fundación Cardiovascular de Colombia. Dr Serrano participated in choosing of the biomarkers and the processing design for the biological samples.

Principal investigator

Anderson Bermon, MD, MSc: associate researcher and epidemiologist at Fundación Cardiovascular de Colombia, Demography and Biostatistics PhD student at CES University. Dr. Bermon participated in the trial design and studied the impact of the results in Colombia, considering the healthcare system limitations.

Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor Faculty of Psychology, Pontificia Bolivariana University. Dr. Uribe designed the message intervention and studied the behavioural theories that support the intervention methodology.

Study chair

Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University College London at Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas conceived the idea of conducting the trial and participated in the methodology design of the trial.

Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived the idea of conducting the trial and participated in the methodology design of the trial.

Sub-investigators:

Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research Department of Primary Care and Population Health, University College London. Dr. Murray contributed in the intervention design and message validity process.

David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the statistical analysis and data management of the trial.

Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and participated in the validity process of the message intervention.

Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins contributed in the message intervention design.

Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of Pharmacy, University College London. Dr. Horne participated in the validity process of the message intervention and choosing adherence scales.

Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the processing design for biological samples.

Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.

Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez participated in the intervention design.

Acknowledgments statement

We thank the Cardiology Department medical staff at Fundación Cardiovascular de Colombia for their help with developing our research questions.

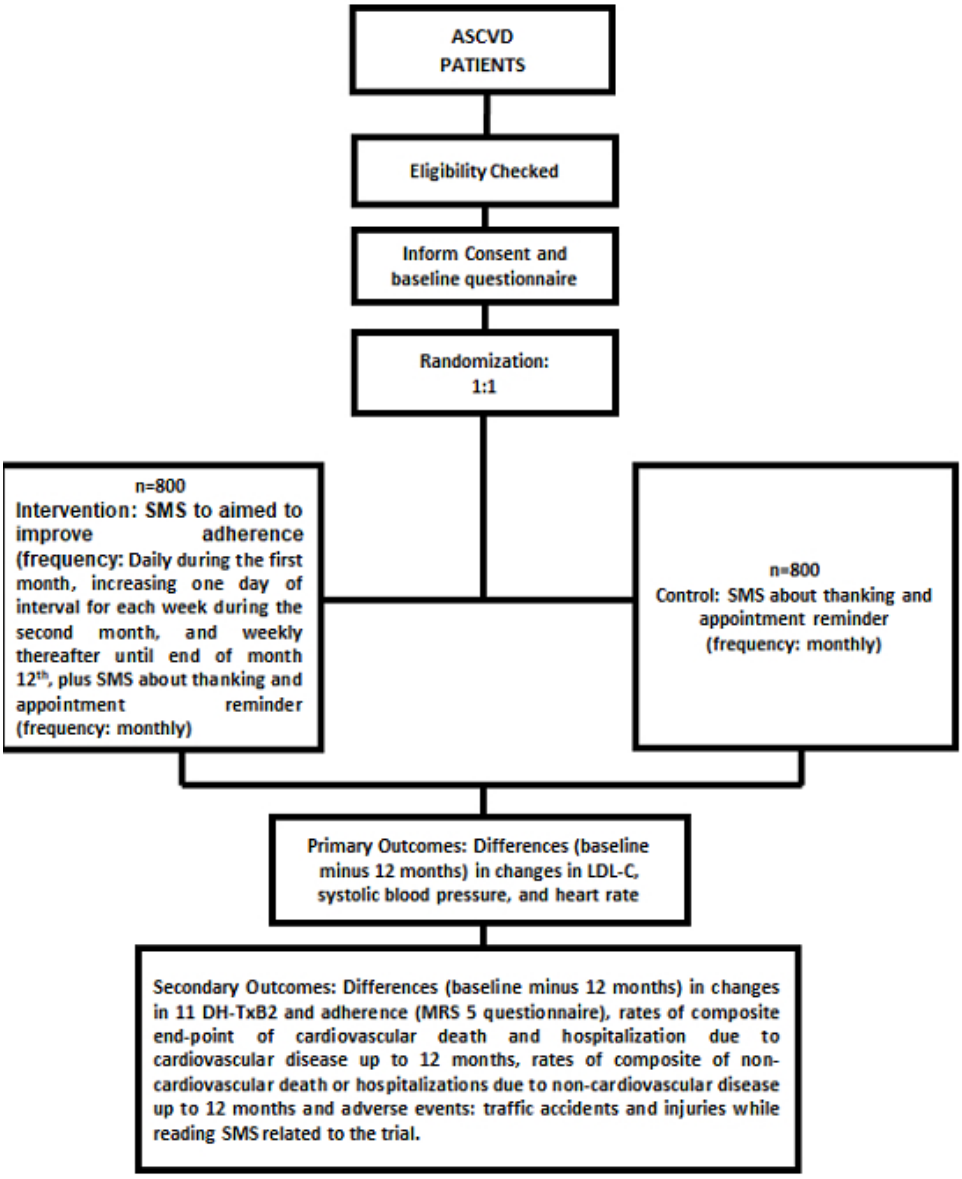
Funding statement

This work was supported by COLCIENCIAS code 656672553352 grant 899-2015

Fundación Cardiovascular de Colombia, Floridablanca
London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded Reference MR/N021304/1
Universidad Pontificia Bolivariana, Bucaramanga sectional

Competing interests' statement

All authors declare there is not conflict of interest.
All funding institutions declare there is not conflict of interest.


ASCVD PATIENTS
Eligibility Checked
Inform Consent and baseline questionnaire
Randomization: 1:1
n=800
Intervention: SMS to aimed to improve adherence (frequency: Daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th, plus SMS about thanking and appointment reminder (frequency: monthly)
n=800
Control: SMS about thanking and appointment reminder (frequency: monthly)
Primary Outcomes: Differences (baseline minus 12 months) in changes in LDL-C, systolic blood pressure, and heart rate
Secondary Outcomes: Differences (baseline minus 12 months) in changes in 11 DH-TxB2 and adherence (MRS 5 questionnaire), rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months, rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months and adverse events: traffic accidents and injuries while reading SMS related to the trial.

Flowchart

Supplementary file

Trial Summary

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT03098186
Date of registration in primary registry	March 10, 2017
Source(s) of monetary or material support	Departamento Administrativo de Ciencia, Tecnología e Innovación Colombia COLCIENCIAS Fundación Cardiovascular de Colombia London School of Hygiene and Tropical Medicine University College, London Universidad Pontificia Bolivariana
Primary sponsor	COLCIENCIAS Contact: contacto@colciencias.gov.co (+57) (1) 6258480 ext. 2081
Secondary sponsor (s)	Fundación Cardiovascular de Colombia
Contact for public queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Contact for scientific queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Public title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol
Scientific title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Countries of recruitment	Colombia
Health condition(s) or problem(s) studied	Acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation) Stable angina Ischemic cerebrovascular disease Peripheral arterial disease
Interventions	Active treatment: will consist of SMS that are aimed to modified behavioural factors associated with poor adherence to cardiovascular medications used in secondary prevention. The SMS will be delivered daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th. In addition, they will receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly. Control: participants will only receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly.
Key inclusion and exclusion criteria	Inclusion Criteria: Age ≥18 years old Sexes eligible for study: both History of at least one of the following arterial occlusive events: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Own at least one mobile phone

	Ability to read and understand text messages (SMS) Intention to stay in the country of recruitment during the next 12 months Exclusion Criteria: Contraindication to take all cardiovascular medications used in secondary prevention. Participation in another randomized clinical trial that could interfere with adherence to treatment.
Study type	Two-parallel arm, only-blind, individually randomized controlled trial.
Date of first enrolment	April 2017
Target sample size	1600
Recruitment status	Recruiting
Primary outcome(s)	Differences in changes (baseline minus 12 months) of: Low density lipoprotein cholesterol (LDL-C) Systolic Blood pressure Heart Rate
Key secondary outcomes	Differences in the changes (baseline minus 12-months) of: (i) Adherence to cardiovascular medications used in secondary prevention measured by MARS-5 questionnaire; and (ii) Urinary levels of 11 dh-TxB2. Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months. Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months Adverse events: traffic accidents and injuries while reading SMS related to the trial.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#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	18
Roles and responsibilities: committees	#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)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies	5

		(published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	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, non-inferiority, exploratory)	7
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	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)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	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)	9
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	11

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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	12
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	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	13

		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	
Data collection plan: retention	#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	13
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	14
Statistics: outcomes	#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	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#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)	14
Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15

formal committee		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	
Data monitoring: interim analysis	#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	15
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
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)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
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	16
Dissemination policy: trial results	#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	17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	17

reproducible research		participant-level dataset, and statistical code	
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16
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	13

BMJ Open

Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028017.R4
Article Type:	Protocol
Date Submitted by the Author:	02-Nov-2019
Complete List of Authors:	Bermon Angarita, Anderson; Fundacion Cardiovascular de Colombia, Research; CES University Uribe Rodríguez, Ana; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Pérez-Rivero, Paula; Universidad Pontificia Bolivariana - Seccional Bucaramanga, Faculty of Psychology Prieto-Merino, David; London School of Hygiene & Tropical Medicine Cáceres Rivera, Diana ; Universidad Cooperativa de Colombia, Nursing Guio, Elizabeth; Fundacion Cardiovascular de Colombia, Metabolism and Genoma Laboratory Atkins, Louise; University College London Research Department of Epidemiology and Public Health Horne, Robert; University College London Murray, Elizabeth; University College London, Primary Care and Population Health Serrano Díaz, Norma; Fundación Cardiovascular de Colombia, Direction of research Free, Caroline; London School of Hygiene and Tropical Medicine, Public Health interventions Unit Perel, Pablo; LSHTM, EPH Casas, Juan Pablo ; University College London Medical School, Clinical Epidemiology and Informatics ; Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Research
Primary Subject Heading:	Public health
Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: The Txt2heart-Colombia randomized controlled trial protocol

Anderson Bermon*
Fundación Cardiovascular de Colombia
Research department
Av. 5 # 6-33, Floridablanca, Santander, Colombia.
Postal code: 681004
Telephone number: (+57) 3002053041
FAX: (+57) 6796470
andersonbermon@fcv.org
*Corresponding author

Ana Fernanda Uribe Rodríguez
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

Paula Fernanda Pérez-Rivero
Faculty of Psychology
Pontificia Bolivariana University,
Floridablanca, Santander, Colombia

David Prieto-Merino
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine
London, UK

Diana Isabel Cáceres Rivera
Cooperativa Colombia University
Faculty of Nursing
Bucaramanga, Santander, Colombia

Elizabeth Guio
Metabolism and Genome Laboratory
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Lou Atkins
Faculty of Health Psychology
University College London
London, UK.

Robert Horne
Centre for Behavioural Medicine
UCL School of Pharmacy
University College London
London, UK.

Elizabeth Murray
Research Department of Primary Care and Population Health
University College London

London, UK.

Norma Cecilia Serrano Díaz
Research Department
Fundación Cardiovascular de Colombia
Floridablanca, Santander, Colombia

Caroline Free
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Pablo A. Perel
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine
London, UK.

Juan P. Casas
Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
VA Boston Healthcare System
Boston, Massachusetts, USA.

Keywords: Cardiovascular diseases, Health behavior, Medications adherence, mHealth, text messaging

Word count: 5006

Abstract

Introduction: Anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that adherence to these cardiovascular medications is far from ideal. A recent Cochrane review showed a potential beneficial effect of SMS interventions on adherence to medication in ASCVD patients.

Methods and analysis: The Txt2heart study is a pragmatic randomized single-blind controlled trial. The objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobile phones to improve adherence to cardiovascular medications in patients with ASCVD. The intervention consists of behavioural techniques delivered via SMS. The primary outcome is change in blood serum low-density lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins. Secondary outcomes will include systolic blood pressure as an indicator of adherence to blood-lowering therapies and heart rate as an indicator of adherence to beta-blockers, urine levels of **11**-dehydrothromboxane B2 (11dhTxB2), self-reported adherence to cardiovascular medications and rates of cardiovascular death or hospitalization due to cardiovascular disease.

Ethics and dissemination: The study will be performed in compliance with the protocol, regulatory requirements, Good Clinical Practice and ethical principles of the Declaration of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to

evaluate whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the local health authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

Trial registration number: ClinicalTrials.gov: NCT03098186

Strengths and limitations of this study.

The trial uses an innovative intervention through SMS methodology based on behaviour theories.

The trial uses biomarkers to evaluate medication adherence.

The trial is the largest evaluating SMS to increase adherence for cardiovascular secondary prevention

Measuring adherence is challenging; we are triangulating data from biomarkers and self-reported adherence to improve the accuracy of the trial measure of effect

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death worldwide. Approximately 35 million people worldwide have an acute coronary event or cerebrovascular event annually, and one quarter of these events occur in people with established ASCVD[1]. These arterial occlusive events occur at an early age in low and middle-income countries (LMICs), which affects economically active populations and results in large economic impacts[2].

Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the risk of ASCVD events in patients with established ASCVD, and these agents are included in the list of the World Health Organization (WHO) Essential Medicines List (EML)[3]. Treatment with these four proven medications (together with smoking cessation) prevents or postpones approximately 75-80% of recurrent vascular events and their complications, such as death and disability[4].

Unfortunately, there is abundant evidence that the worldwide adherence to these cardiovascular medications in patients with ASCVD is far from ideal. Less than half of patients with known ASCVD disease in high-income countries are receiving this group of cardiovascular medications, and the situation is much worse in LMICs. The PURE

study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types of cardiovascular drugs[5].

A wide range of socio-economic and service level factors influence whether patients obtain medications, including the availability of medication (drugs out of stock), the lack of affordable medication and service factors, such as the availability and training of health care providers. Adherence to medication focuses on whether patients take the prescribed medication. Two recent systematic reviews on patient factors that affect adherence to ASCVD medications in secondary prevention showed that these factors go far beyond simply "forgetting" to take the medication and include a range of factors, including patients' perceptions of the cause and prognosis of the illness (e.g., fatalistic perceptions or absence of symptoms) and/or the risks and benefits of medications (e.g., fear of side effects or concern about multiple medications), the patient-physician relationship, availability of family/social network support, and comorbidities (e.g., depression)[6 7].

A recent systematic review from RCTs on interventions to improve adherence to medications in patients with ASCVD demonstrated several potential interventions, and importantly, simple interventions may be as effective as complex ones (and therefore easier to replicate)[8]. However, this review also highlighted many limitations in the current evidence, such as risk of bias, small sample sizes and lack of studies in LMICs, where most of the patients with ASCVD live. Among the most promising simple strategies to increase adherence, this review singled out Short Message Service (SMS) interventions.

Mobile phones have become an "essential" instrument of daily life worldwide, with approximately 7 billion subscribers, of whom 78% are based in LMICs[9]. This use makes mobile phones an "ideal instrument" to deliver health behaviour change interventions to large numbers of people at a low cost. Systematic reviews of RCTs using mHealth interventions confirm that SMS can be successful in changing behaviour, including smoking cessation and improved adherence to HIV medications[1011]. Patient factors influencing adherence, such as knowledge attitudes and beliefs, could be amenable to change using mobile phone messages sent to patients.

A recent Cochrane review evaluated the effects of SMS on adherence to medications in patients with ASCVD[12]. The review identified seven trials (1310 participants) and showed a beneficial effect of SMS on adherence to medications in six of these trials. However, the quality of the evidence was very low. The Cochrane review identified the following limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV) most studies recruited only patients with acute coronary syndrome, which

leaves out an important group of patients with other arterial occlusive events (e.g., ischaemic stroke, peripheral vascular disease and programmed coronary revascularizations) who should be amenable for this type of intervention; (V) few studies were performed in LMICs; and (VI) most trials did not describe the processes behind the SMS content generation, and the few trials that did report these processes did not target the key knowledge and attitudinal factors that are known to influence adherence to medication; instead the interventions were simple "reminders".

In conclusion, given the high prevalence of people with ASCVD in LMICs and the low use of cost-effective secondary prevention medications, a low-cost intervention that builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to improve public health. The current evidence shows that SMS interventions based on behaviour-change techniques are a potentially effective strategy to increase adherence to medications in people with ASCVD. However, further large trials are needed.

To provide the high-quality evidence needed to assess the effect of SMS interventions based on behaviour-change techniques to increase adherence to medications in patients with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the efficacy and safety of SMS on adherence to cardiovascular medications. The trial is being performed in a setting (Colombia) where patient factors, such as knowledge, attitudes and beliefs, are important determinants of adherence. In this context, medicines are widely available and generally affordable, so an intervention delivered to patients via SMS has the potential to be effective.

METHODS AND ANALYSIS

This protocol is reported following the SPIRIT Standard Protocol Items recommendations for Interventional Trials[13] (see supplementary file 1).

Aim and objectives

The primary objective is to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobiles phones to improve adherence to cardiovascular medications in patients with atherosclerotic cardiovascular disease (ASCVD). We will assess the intervention efficacy via the measurement of blood serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as

an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart rate as an indicator of adherence to beta-blockers.

The secondary objective is to assess the impact of mobile text messaging on self-reported adherence to medications, hospitalizations, and the composite end-point of incident Major Adverse Cardiovascular Events (MACE) at 12 months.

Choice of comparator

The trial design is a two-parallel arm in which the comparator is a control follow up. Patients allocated to the control group will receive monthly messages that convey the gratitude of the research team for their participation and emphasize the importance of follow up. The choice of comparator was guided by considerations of enhancing acceptability of the trial and enhancing retention and follow-up rates, while not materially altering medication-taking behaviours or causing participants harm or discomfort. Participants will be told that they could be allocated to one of two different groups. Furthermore, our intervention will not interfere with medical treatment. Patients will be warned that the study does not replace medical assistance and that they must continue with their traditional treatment.

Trial design

Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled trial. This design is aimed to minimize any potential bias that affects the internal validity of the study. The selection criteria were designed to increase the number of potential beneficiaries of the intervention and to keep the selection process as close as possible to the future scenario in which the intervention will be implemented. Therefore, Txt2THeart-Colombia is pragmatic in design. The active intervention will be the SMS delivered to mobile phones, and the content of the SMS is aimed to modify behaviours associated with poor adherence to ASCVD medications in ASCVD patients. Randomization will be performed as block randomization with a 1:1 allocation.

Study setting

We will recruit patients at Fundación Cardiovascular in Colombia, which has a staff that is knowledgeable in trials and a sufficient pool of eligible patients. The trial will continue to add sites, if necessary, to ensure that the sample size is achieved. There is no limit to the maximum number of patients to be recruited in each site.

Eligibility criteria

Inclusion criteria: Adult patients ≥18 years old with a history of at least one of the following arterial occlusive events will be included: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischaemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Patients should own a mobile phone and be able to read SMS.
Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular secondary prevention medications.

Intervention

The intervention under evaluation consists of *behavioural change techniques* (BCTs) delivered via SMS. We developed our intervention following the recommendations of Abroms et al[14]. First, we reviewed the literature on individual level factors that influence adherence to medication. We performed country-specific qualitative studies using focus group discussions and semi-structured interviews to evaluate cardiovascular patients' perceptions about mHealth programmes to determine the necessary content and preferred timing and frequency of the SMS messages. To construct the content of the SMS, we wrote messages using educational and enabling behaviour change functions and established BCTs to target the potentially modifiable factors that influence the adherence referred to in the literature and found in our qualitative studies[15]. Finally, we tested the SMS messages with participants and adapted the messages based on their feedback to ensure the messages were understandable, acceptable, and relevant[16]. The resultant intervention delivered by SMS provides information about health consequences of adherence or non-adherence, instruction on how to take medication, medicine-taking prompts and cues, support in establishing medicine-taking habits, reframing medicine-taking and provides or encourages social support for taking medication[17]. The messages were designed according to the Transtheoretical Model (TTM) (Prochaska & DiClemente, 1992) and were aimed to enhance actions related to the steps and processes of this model. We will send messages daily the first month, three times per week the second month and once weekly the last ten months. This reducing frequency is consistent with the TTM, which suggests that people in the early stages of change require more intense input than people in later stages. In accordance with data from the focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The intervention will be delivered through an electronic platform, and it will be a one-way intervention. We will explain patients that they should not answer the messages, but they will be able to request to stop receiving the messages and withdraw from the trial by sending a message with the word "STOP". We will explain to patients that they should

send the 'stop' message in this situation. Stop messages will be saved and monitored by a trained engineer, separate from the study team, in order to maintain blinding. Similarly, a trained engineer, separate from the study team, will save and monitor the patients' answers if they respond to the messages. Because of the pragmatic nature of our study we will not tailor the messages. The trial intervention will start the day after recruitment and continue for 12 months or until the participant withdraws from the study or dies. The follow-up duration will be at least 12 months to a maximum of 36 months. Participants will not receive messages after month 12.

Outcomes

The primary outcome was selected for its clinical relevance and include: differences in changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of adherence to statins.

The following secondary outcomes will be included: *systolic blood pressure* as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs), *heart rate* as an indicator of adherence to beta-blockers*, urine levels of 11 dhTxB2* as an indicator of adherence to antiplatelet therapy; *self-reported adherence to cardiovascular medications* used in secondary prevention as measured using the MARS-5 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular disease and non-cardiovascular death or hospitalizations due to non-cardiovascular disease. We will also include road traffic crashes (the only potential known hazard of text messaging) and death due to all causes as secondary outcomes.

Participant timeline

Participants who fulfil the eligibility criteria and provide their informed consent will be recruited into the txt2heart trial. After the participant provided informed consent, baseline characteristics will be collected at the first visit using questionnaires (MARS-5 and PHQ-9 Patient Health Questionnaire), blood samples, blood pressure, and heart rate. Participants will be randomized to the intervention or control arm. The trial intervention will start the day after recruitment and will continue for 12 months to a maximum of 36 months, or when the participant withdraws from the study, or dies. We will perform a phone follow-up interview three months later, during the second visit, to evaluate adequate SMS delivery and the occurrence of clinical events. Finally, we will collect data on self-reported adherence to cardiovascular medications (MARS-5), blood pressure, heart rate and clinical end-points in the third visit (12 months later). The 12-month follow up marks the primary outcome point. For patients with follow up beyond 12 months, we

will perform (by phone) assessments of clinical outcomes (death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization) every 6 months until 36 months, the longest available follow-up (figure 1).

Figure 1.

Trial flowchart

Sample Size

The sample size of the study is 1600 participants. The power of the study was calculated for differences between arms in the reduction in the primary outcome LDL-C (12-month minus baseline).

The power of the study was calculated for the primary outcome of the clinical trial, i.e., differences in the levels of physiological markers of adherence to cardiovascular drugs. Because the power of a sample size depends on several parameters in this study, such as the doses are finally prescribed to patients and what proportion of patients will adhere, we performed several power and sample size calculations for different scenarios. We concluded that 1600 was a reasonable sample size. For example, assuming that adherent patients to 40 mg atorvastatin for 12 months are expected to have an average LDL-cholesterol reduction of 91.3 mg/dL (data derived from randomized clinical trials), and non-adherent patients will reduce LDL-cholesterol by an average of 18.3 mg/dL (or 20% of the reduction in adherent patients) and that the standard deviation of the changes is approximately 27.07 ml/dL, we would have 97% power to detect a 7% difference in adherence between arms or a 77% power to detect a 5% difference (always using a 5% type-I error). However, if patients were on 20 mg atorvastatin and the expected reductions in LDL-C were 80.05 mg/dL in adherent and 16.01 mg/dL in non-adherent patients, then we would have a 91% power to detect a 7% difference of adherence between arms and a 66% power to detect a 5% difference between arms (table 1).

Table 1

Sample size calculations

Statins and its frequency in trials		Reduction in LDL after a year of treatment in adherents and non-adherents			Power to detect differences depending on adherence increase		
	%	**AD=yes**	**AD=No**	**Dif**	**5.0%**	**7.0%**	**10.0%**
Atorvastatin 10	1.5%	1.79	0.36	1.43	53%	82%	98%

Atorvastatin 20	32.9%	2.07	0.41	1.66	66%	91%	100%
Atorvastatin 40	52.4%	2.36	0.47	1.89	77%	97%	100%
Atorvastatin 80	9.4%	2.64	0.53	2.11	85%	99%	100%
Fluvastatin 20 mg	0.0%	1.02	0.20	0.82	21%	37%	64%
Lovastatin 40	0.0%	1.77	0.35	1.42	53%	81%	98%
Pravastatin 10	0.0%	0.95	0.19	0.76	19%	33%	58%
Pravastatin 20	0.0%	1.17	0.23	0.94	27%	46%	76%
Pravastatin 40	0.0%	1.38	0.28	1.10	35%	60%	88%
Rosuvastatin 5	0.0%	1.84	0.37	1.47	56%	84%	99%
Rosuvastatin 10	0.3%	2.08	0.42	1.66	66%	91%	100%
Rosuvastatin 20	1.7%	2.32	0.46	1.86	76%	96%	100%
Rosuvastatin 40	1.6%	2.56	0.51	2.05	83%	98%	100%
Simvastatin 10	0.0%	1.31	0.26	1.05	32%	55%	85%
Simvastatin 20	0.1%	1.54	0.31	1.23	42%	69%	94%
Simvastatin 40	0.2%	1.78	0.36	1.42	53%	81%	98%
Simvastatin 80	0.0%	2.01	0.40	1.61	63%	90%	100%

*Elaborated by the authors

Power is calculated assuming a sample size of 800 per arm, 5% type-I error, a standard deviation of LDL change of 0.7 and that non-adherent patients will still reduce their LDL on average 20% of the reduction in adherent patients.

Interpretation of the table: Example of third line (atorvastatin 40): 52.4% of patients in the hospital take atorvastatin 40. Adherent patients are expected to reduce their cholesterol an average of 2.36 mmol/l in the first year, and non-adherent patients are expected to reduce it 0.47 mmol/l. If all patients were on atorvastatin 40, we would have a 77% power to detect a true increase in adherence of 5%, a 97% power to detect a true increase in adherence of 7% and almost a 100% power to detect a true increase in adherence of 10%. Atorvastatin is the most prescribed statin in patients in our study. About the 65% of the sample use.

Recruitment

The pragmatic nature of this trial will allow collaborators to follow different strategies for participant recruitment according to the setting. There are three main approaches for the recruitment of patients who fulfil the inclusion criteria a) in hospital patients at the time of discharge, b) patients attending outpatient clinics, c) and patients who are in the health care facility database and who will be contacted by phone calls and recruited in outpatient clinics.

Assignment of intervention

Randomization: We will use block randomization (varying size), stratifying by centre and with 1:1 allocation between the intervention and control arm. Randomization will be performed centrally using the CommCare platform after eligibility criteria was confirmed, informed consent signed, and baseline information collected. Therefore, the randomized allocation will not be revealed until after a participant was formally entered into the trial. Therefore, concealment of allocation will be complete. The SMS will be automatically generated by the CommCare platform and unknown to the investigators in contact with patients.

Blinding: Because of the nature of the intervention (SMS messages), it is not possible to include blind participants. However, the tx2theart trial will perform a blinded assessment of outcomes. Research personnel collecting data on clinical events, adherence scales, and biomarkers will not have access to treatment allocation. The laboratory results will be performed once trial follow-up is completed.

Data collection methods

Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered in the CommCare platform, designed by Dimagi. CommCare is an open source mobile platform designed for data collection, client management, decision support, and behaviour change communication. The electronic devices (desktop computers, laptops and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by Fundación Cardiovascular de Colombia.

Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while maximizing retention to follow-up. The following strategies to prevent loss to follow-up will be used. 1) One phone call at the third month of participation. Trained personnel different from the other interviewers will phone the participants to guarantee the blind design. Professionals in charge of the follow-up are trained in patient contact with the ability to empathize with volunteers. 2) We will register at least three relatives' numbers to contact in case we are not able to reach the patient, and we will phone the participant's relatives. 3) We will register the addresses of participants in case we cannot reach the patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the participants a contact phone number to let us to know if they change their phone number contact. We will explain these strategies to participants to get permission for further contact.

Clinical outcomes

Death from cardiovascular causes and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent revascularization will be defined by local investigators based on clinical notes and clear objective criteria using the suggestions provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials[18].

Self-reported adherence

To estimate adherence, we will use a self-reported scale named Medication Adherence Report Scale 5 (MARS-5), which is a valid and reliable scale for measuring adherence to medication in chronic conditions at trial entry and at the final assessment at 12 months[19]. The MARS-5 Scale elicits patients' reports of non-adherence. To diminish the social pressure on patients to report high adherence, items are phrased in a non-threatening manner, and patients are assured that their responses will be anonymous and confidential. Participants are asked to rate the frequency with which they engaged in each of five aspects of non-adherent listed behaviours (e.g., 'I forget to take these medicines', 'I stop taking these medicines for a while') using a 5-point scale ranging from 'never' to 'always'. Scores for each item are summed to give a total score that ranged from 5 to 25, with higher scores indicating higher levels of adherence. Patients will be recruited at least 30 days, after discharge in the case of their first cardiovascular event.. A trained psychologist will administer the MARS-5 during the first interview.

In order to complete information about medications, we will ask patients about prescribed medication.

Biomarkers

Physiological measurements of heart rate and blood pressure will be measured using a calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by trained health care professionals. Patients will sit quietly for 10 minutes before the examinations.

Blood LDL-C: Quantification of serum LDL will be performed using automated equipment by a direct method.

Recent large epidemiological studies confirmed that resting heart rate is an independent predictor of cardiovascular mortality. Heart rate decrease is itself an important mechanism of the benefit of the blockers and other drugs that reduce heart rate after an acute myocardial infarction[(1–4)]. Controversies on the optimal dose to obtain results remain, but the reduction in heart rate is notorious in patients receiving beta-blockers[5]. In Colombia, beta-blockers are a first-line drug used for secondary prevention. The most

frequently beta-blocker is carvedilol, which exhibits advantages in decreasing heart rate and mortality in patients with some type of cardiovascular event[6].

Data management

Data will be stored on a secure system and will be password protected. All trial procedures will be performed in accordance with the principles of Good Clinical Practice (GCP). Essential documents of the sponsor/trial organizers and investigators will be retained for at least 10 years after completion of the trial. The research staff will maintain appropriate medical and research records for this clinical study and meet with the regulatory and institutional frameworks for the protection of the confidentiality requirements. As sponsor of this trial, Fundación Cardiovascular de Colombia will allow regulatory agencies to examine (under applicable law) clinical records to check the quality, safety and progress of the study.

Statistical Analysis

The main analyses will be an "intention to treat", meaning it will compare all patients allocated to the intervention to patients allocated to the control arm, regardless of whether they received the allocated intervention. A sensitivity per protocol analysis will also be performed. For continuous outcomes (including: LDL cholesterol, blood pressure and Heart rate), we will estimate an ANCOVA model regressing the 12-month difference from baseline in the allocated group and the mean centred baseline values of the continuous variable. Deaths and hospitalizations will be analysed using Cox regression models to estimate hazard ratios. The assumptions underlying all of these models will be assessed. For subgroup analyses, we will only consider a limited number of variables that, given the mechanism of action of the intervention, could modify the effect of the intervention. A detailed statistical analysis plan setting out full details of the proposed analyses will be prepared and completed before the trial database is locked for final analysis. Missing data will be managed by an intention to treat analysis.

Data Monitoring

Data monitoring will be executed according to GCP Guidelines. This trial is a large, pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change behaviour and increase adherence of safe and proven effective interventions for secondary prevention that have been in clinical use for decades. Clinical management for underlying conditions will remain as per hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring because of participation in this research study was assessed as low risk to

participants in each of these categories. Based on the low risks associated with this trial, there will not be a data monitoring committee. However, a monitoring plan to ensure appropriate performance of the trial will be developed, which will incorporate 100% central monitoring in conjunction with procedures, such as investigator training and meetings and written guidance. All data will be subject to statistical monitoring, and at least 10% of data will be subjected to on-site monitoring. Investigators/institutions are required to provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review and regulatory inspection. All trial-related and source documents must be kept for 15 years after the end of the trial.

Patient and Public Involvement

We did not directly include PPI in this study. However, to design the intervention, we interviewed patients about their perceptions of e-health and their previous experience with mobile cellular phone technology and obtained their feedback about the messages in the intervention. The Ethics Committee evaluated and approved our research included patient representatives.

ETHICS AND DISSEMINATION

Protocol amendments

We redefined systolic blood pressure and heart rate as secondary outcomes because we do not have calculation power for these measures. In the first version of protocol, these measures were primary outcomes.

Ethical considerations

The study will be performed in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki.

Ethical approval

The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial.

Informed Consent:

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient will be given every opportunity to clarify any points he/she does not understand

and, if necessary, ask for more information. Written consent must be given by the patient and/or the legal guardian of the patient after detailed information about the study is provided in accordance with any national provisions on the protection of clinical study patients. The verbal explanation will cover all of the elements specified in the written information provided to the patient. Patients and/or legal guardians will be required to sign and date the informed consent form. Patients who refuse to give or who withdraw written informed consent will not be included or continue in the study. The trial will include a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or law of protection of personal data, where the study team is authorized to handle personal and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be recorded and stored for a set time. Eligible participants will only be included in the study after signing “Txt2Heart-Colombia” informed consent (testified, where required by law or regulation), as approved by the ethics committees. The process will be documented in the patient source documents, specifically in CRFs (Case Report Form).

Confidentiality: Information about the study subjects will be kept confidential. The investigators will ensure the anonymity of patients, and patients will not be identified by name in any document. Informed consent forms and patient recruitment registration will be kept strictly confidential only to permit identification of the patient at Fundación Cardiovascular de Colombia. Information about the study subjects will be handled under the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law of data protection). The regulations that require an authorization signed by the patient including the follow information: What protected health information (PHI) will be collected from the study subjects, who will have access to that information and why, who will use and disclose that information and the right to withdraw his/her authorization to use their PHI.

Access to data

The principal investigator and sub-investigators will have access to the data to verify and analyse the results. To ensure confidentiality, all of the investigators will be blinded of participant identification.

Ancillary and post-trial care

Due to its low risk, the intervention in this trial will not include insurance for participants. However, we will refer patients to their medical services in case we think that they need

assistance. Furthermore, a full explanation of the scope and limitations of the study will be told to the patients before they sign the informed consent.

Dissemination policy

The Txt2heart Colombia trial is aimed to provide high level evidence that evaluates whether SMS messages delivered through mobile telephones change the behaviour of Colombian patients who have suffered a cardiovascular event. Trial results will be presented to the health local authorities, and if the intervention is effective and safe, we hope this strategy will be implemented quickly because of its low cost and wide-reaching impact on the population.

The results from the trial will be published in an open journal to provide scientists, clinicians and policymakers access to the data.

Limitations

Because, it is probably that most of patients will start the study already on statins, the LDL changes need to be evaluated with caution considering participants' start point. Likewise, power calculation is based on pre versus post statin treatment, rather than on-therapy at baseline changes. Regarding heart rate and blood pressure, because there is not power calculation; comparing entry and exit measures is limited. Finally, adherence measures are limited because we will not establish a baseline and we must consider self-reported scales downsides.

REFERENCES

1. Perel, P., et al., *Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease: The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease.* Glob Heart, 2015. **10**(2): p. 99-110.
2. Perel, P., et al., *Noncommunicable diseases and injuries in Latin America and the Caribbean: time for action.* PLoS Med, 2006. **3**(9): p. e344.
3. World Health Organization. *Model List of Essential Medicines (20th List)*. 2017 [cited [Accessed June 23 2017]; Available from: http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.
4. Yusuf, S., *Two decades of progress in preventing vascular disease.* Lancet, 2002. **360**(9326): p. 2-3.
5. Yusuf, S., et al., *Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey.* Lancet, 2011. **378**(9798): p. 1231-43.

6. Rashid, M.A., et al., *Medication taking in coronary artery disease: a systematic review and qualitative synthesis.* Ann Fam Med, 2014. **12**(3): p. 224-32.
7. R.M., *Patient factors that influence cardiovascular medication adherence (MSc Thesis)*. 2014, London School of Hygiene & Tropical Medicine.
8. Santo, K., et al., *Interventions to improve medication adherence in coronary disease patients: A systematic review and meta-analysis of randomised controlled trials.* Eur J Prev Cardiol, 2016. **23**(10): p. 1065-76.
9. International Telecommunications Union. *ICT Facts and figures*. 2014 [cited [Accessed July 20, 2017]; Available from: http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2014-e.pdf.
10. Free, C., et al., *The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review.* PLoS Med, 2013. **10**(1): p. e1001362.
11. Catalani, C., et al., *mHealth for HIV Treatment & Prevention: A Systematic Review of the Literature.* Open AIDS J, 2013. **7**: p. 17-41.
12. Adler, A.J., et al., *Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2017. **4**: p. Cd011851.
13. Chan, A.W., et al., *SPIRIT 2013 statement: defining standard protocol items for clinical trials.* Ann Intern Med, 2013. **158**(3): p. 200-7.
14. Abroms, L.C., et al., *Developing and Pretesting a Text Messaging Program for Health Behavior Change: Recommended Steps.* JMIR Mhealth Uhealth, 2015. **3**(4): p. e107.
15. Michie, S., et al., *The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions.* Ann Behav Med, 2013. **46**(1): p. 81-95.
16. Moore, G.F., et al., *Process evaluation of complex interventions: Medical Research Council guidance.* BMJ, 2015. **350**: p. h1258.
17. Uribe-Rodríguez, A., et al., *Designing a text messaging program to increase adherence to medication for the secondary prevention of cardiovascular disease.* medRxiv **19002683**; doi: https://doi.org/10.1101/19002683
18. Hicks, K.A., et al., *2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards).* Circulation, 2015. **132**(4): p. 302-61.
19. Mahler, C., et al., *Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany.* J Eval Clin Pract, 2010. **16**(3): p. 574-9.

Authors' contributions

Study director

Norma Cecilia Serrano Díaz, MSc: Senior researcher and Research Department Director at Fundación Cardiovascular de Colombia. Dr Serrano participated in choosing of the biomarkers and the processing design for the biological samples.

Principal investigator

Anderson Bermon, MD, MSc: associate researcher and epidemiologist at Fundación Cardiovascular de Colombia, Demography and Biostatistics PhD student at CES University. Dr. Bermon participated in the trial design and studied the impact of the results in Colombia, considering the healthcare system limitations.

Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor Faculty of Psychology, Pontificia Bolivariana University. Dr. Uribe designed the message intervention and studied the behavioural theories that support the intervention methodology.

Study chair

Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University College London at Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas conceived the idea of conducting the trial and participated in the methodology design of the trial.

Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived the idea of conducting the trial and participated in the methodology design of the trial.

Sub-investigators:

Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research Department of Primary Care and Population Health, University College London. Dr. Murray contributed in the intervention design and message validity process.

David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the statistical analysis and data management of the trial.

Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and participated in the validity process of the message intervention.

Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins contributed in the message intervention design.

Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of Pharmacy, University College London. Dr. Horne participated in the validity process of the message intervention and choosing adherence scales.

Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the processing design for biological samples.

Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.

Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez participated in the intervention design.

Acknowledgments statement

We thank the Cardiology Department medical staff at Fundación Cardiovascular de Colombia for their help with developing our research questions.

Funding statement

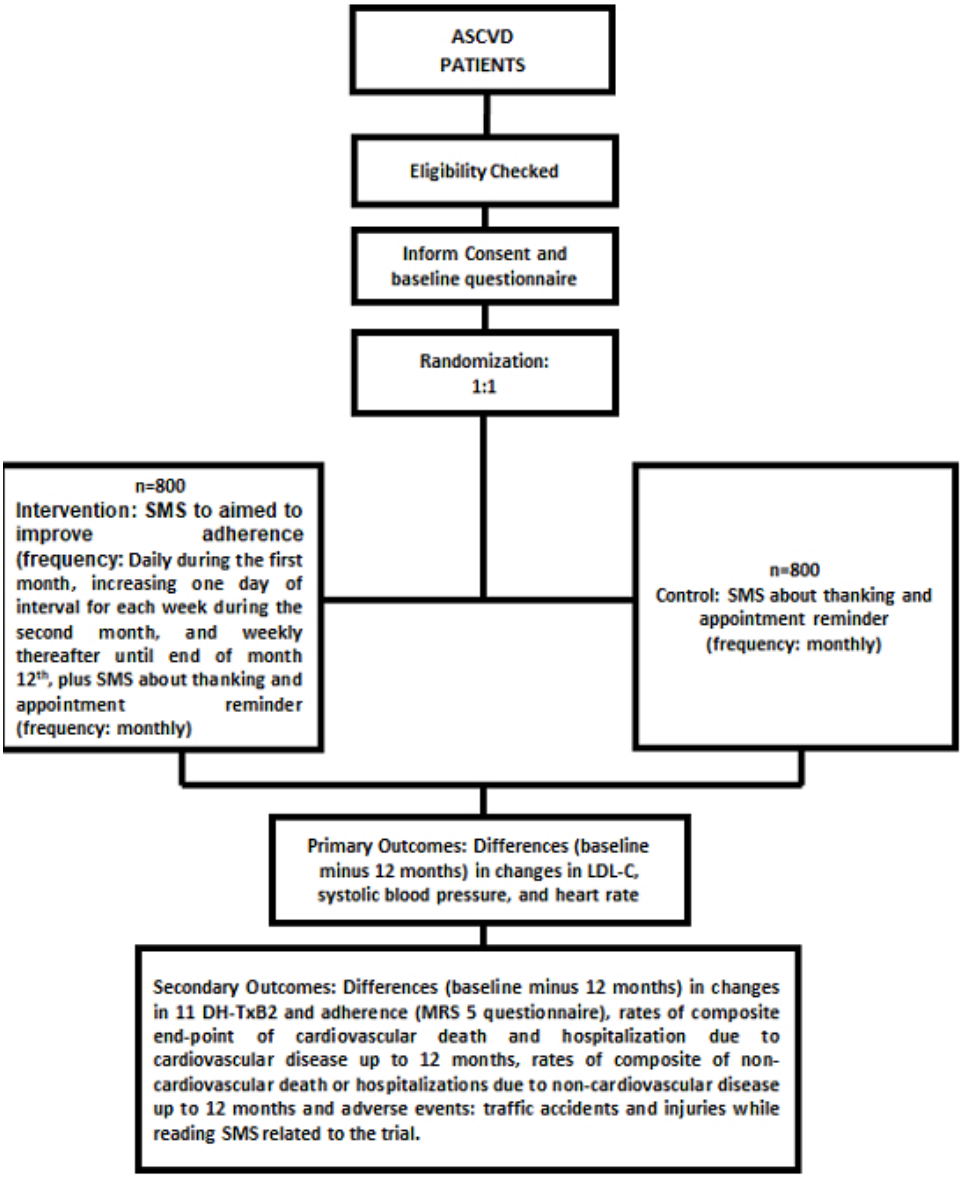
This work was supported by COLCIENCIAS code 656672553352 grant 899-2015

Fundación Cardiovascular de Colombia, Floridablanca
London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded Reference MR/N021304/1
Universidad Pontificia Bolivariana, Bucaramanga sectional

Competing interests' statement

All authors declare there is not conflict of interest.

All funding institutions declare there is not conflict of interest.


ASCVD PATIENTS
Eligibility Checked
Inform Consent and baseline questionnaire
Randomization: 1:1
n=800
Intervention: SMS to aimed to improve adherence (frequency: Daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th, plus SMS about thanking and appointment reminder (frequency: monthly)
n=800
Control: SMS about thanking and appointment reminder (frequency: monthly)
Primary Outcomes: Differences (baseline minus 12 months) in changes in LDL-C, systolic blood pressure, and heart rate
Secondary Outcomes: Differences (baseline minus 12 months) in changes in 11 DH-TxB2 and adherence (MRS 5 questionnaire), rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months, rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months and adverse events: traffic accidents and injuries while reading SMS related to the trial.

Flowchart

Supplementary file

Trial Summary

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT03098186
Date of registration in primary registry	March 10, 2017
Source(s) of monetary or material support	Departamento Administrativo de Ciencia, Tecnología e Innovación Colombia COLCIENCIAS Fundación Cardiovascular de Colombia London School of Hygiene and Tropical Medicine University College, London Universidad Pontificia Bolivariana
Primary sponsor	COLCIENCIAS Contact: contacto@colciencias.gov.co (+57) (1) 6258480 ext. 2081
Secondary sponsor (s)	Fundación Cardiovascular de Colombia
Contact for public queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Contact for scientific queries	Anderson Bermon, MsC. +576399292 ext 344 andersonbermon@fcv.org
Public title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol
Scientific title	Evaluation of the Efficacy and Safety of text messages targeting adherence to cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia randomized controlled trial protocol

Countries of recruitment	Colombia
Health condition(s) or problem(s) studied	Acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation) Stable angina Ischemic cerebrovascular disease Peripheral arterial disease
Interventions	Active treatment: will consist of SMS that are aimed to modified behavioural factors associated with poor adherence to cardiovascular medications used in secondary prevention. The SMS will be delivered daily during the first month, increasing one day of interval for each week during the second month, and weekly thereafter until end of month 12th. In addition, they will receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly. Control: participants will only receive SMS thanking for their participation in the trial, reminders of trial appointment and informing if they have changed contact details. The frequency of this SMS will be monthly.
Key inclusion and exclusion criteria	Inclusion Criteria: Age ≥18 years old Sexes eligible for study: both History of at least one of the following arterial occlusive events: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischemic cerebrovascular disease, peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Own at least one mobile phone

	Ability to read and understand text messages (SMS) Intention to stay in the country of recruitment during the next 12 months Exclusion Criteria: Contraindication to take all cardiovascular medications used in secondary prevention. Participation in another randomized clinical trial that could interfere with adherence to treatment.
Study type	Two-parallel arm, only-blind, individually randomized controlled trial.
Date of first enrolment	April 2017
Target sample size	1600
Recruitment status	Recruiting
Primary outcome(s)	Differences in changes (baseline minus 12 months) of: Low density lipoprotein cholesterol (LDL-C) Systolic Blood pressure Heart Rate
Key secondary outcomes	Differences in the changes (baseline minus 12-months) of: (i) Adherence to cardiovascular medications used in secondary prevention measured by MARS-5 questionnaire; and (ii) Urinary levels of 11 dh-TxB2. Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months. Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months Adverse events: traffic accidents and injuries while reading SMS related to the trial.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#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	18
Roles and responsibilities: committees	#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)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies	5

		(published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	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, non-inferiority, exploratory)	7
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	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)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	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)	9
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	11

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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	12
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	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	13

		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	
Data collection plan: retention	#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	13
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	14
Statistics: outcomes	#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	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#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)	14
Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15

formal committee		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	
Data monitoring: interim analysis	#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	15
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
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)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
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	16
Dissemination policy: trial results	#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	17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	17

reproducible research		participant-level dataset, and statistical code	
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	16
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	13