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# 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

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

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Manuscripts

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3 **Evaluation of the Efficacy and Safety of text messages targeting adherence to**  
4 **cardiovascular Medications in Secondary Prevention: The Txt2heart-Colombia**  
5 **randomized controlled trial protocol**  
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27 **Keywords:** Cardiovascular diseases, Health behavior, Medications adherence,  
28 mHealth, text messaging  
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31 **Word count:** 5309  
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33

### 34 35 **Abstract**

36  
37 **Introduction:** Evidence has shown that in patients with Atherosclerotic cardiovascular  
38 diseases (ASCVD) anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins,  
39 are cost-effective in reducing the risk of ASCVD events. Unfortunately, there is abundant  
40 evidence that adherence to these cardiovascular medications is far from ideal. A recent  
41 Cochrane review showed a beneficial effect of SMS interventions on adherence to  
42 medication in ASCVD patients.  
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44  
45 **Methods and analysis:** Txt2heart study is a pragmatic randomized single blind  
46 controlled trial. The objective is to evaluate the efficacy and safety of an intervention with  
47 SMS messages delivered by mobiles phones to improve adherence to cardiovascular  
48 medications in patients with ASCVD. The intervention consists on behavioural  
49 techniques delivered through SMS. The primary outcomes are: Blood serum LDL-C  
50 levels as an indicator of adherence to statins, systolic blood pressure as an indicator of  
51 adherence to blood-lowering therapies and heart rate as an indicator of adherence to  
52 beta blockers. Secondary outcomes will include: Urine levels of 11 dhTxB2, adherence  
53 to cardiovascular medications and rates of cardiovascular death or hospitalization due  
54 to cardiovascular disease.  
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56  
57 **Ethics and dissemination:** The study will be conducted in compliance with the protocol,  
58 regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki.  
59 The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and  
60 approved the trial. Txt2 heart Colombia trial is aimed to provide high level evidence that

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3 evaluate whether SMS messages delivered through mobile telephony, change the  
4 behaviour of Colombian patients who have suffered a cardiovascular event. Trial results  
5 will be presented to the health local authorities and if the intervention turns out to be  
6 effective and safe, we hope this strategy would be implemented soon considering its low  
7 cost and wide-reach to the population.  
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12 **Trial registration number:** ClinicalTrials.gov: NCT03098186  
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15 **Strengths and limitations of this study.**  
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19 This trial uses biomarkers to evaluate medication adherence.  
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21 This trial uses an innovative intervention through SMS methodology based on behavior  
22 theories  
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24 There is, however a variability in time of biomarkers, therefore we will use two additional  
25 measures to evaluate adherence.  
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29 **Tabla 1.**  
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31 **Summary**  
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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: <a href="mailto:contacto@colciencias.gov.co">contacto@colciencias.gov.co</a> (+57) (1) 6258480 ext. 2081
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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	<p>Inclusion Criteria:</p> <p>Age <math>\geq 18</math> years old</p> <p>Sexes eligible for study: both</p> <p>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).</p> <p>Own at least one mobile phone</p> <p>Ability to read and understand text messages (SMS)</p> <p>Intention to stay in the country of recruitment during the next 12 months</p> <p>Exclusion Criteria:</p> <p>Contraindication to take all cardiovascular medications used in secondary prevention.</p> <p>Participation in another randomized clinical trial that could interfere with adherence to treatment.</p>
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)	<p>Differences in changes (baseline minus 12 months) of:</p> <p>Low density lipoprotein cholesterol (LDL-C)</p> <p>Systolic Blood pressure</p> <p>Heart Rate</p>

Key secondary outcomes	<p>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.</p> <p>Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months.</p> <p>Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months</p> <p>Adverse events: traffic accidents and injuries while reading SMS related to the trial.</p>
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## 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<sup>1</sup>. In low & middle-income countries (LMICs) these arterial occlusive events occur at an early age, affecting economically active populations resulting in large economic impacts<sup>2</sup>.

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)<sup>3</sup>. 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<sup>4</sup>.

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<sup>5</sup>.

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



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3 affordable medication and service factors such as the availability and training of health  
4 care providers. Adherence to medication focuses on whether patient take medication  
5 that is prescribed. Two recent systematic reviews on patient factors that affect adherence  
6 to ASCVD medications in secondary prevention showed that these go far beyond simply  
7 “forgetting” to take medication and include a range of factors including patients’  
8 perceptions of the cause and prognosis of the illness(e.g. fatalistic perceptions or  
9 absence of symptoms) and / or the risks and benefits of medications (e.g. fear of side-  
10 effects or concern about multiple medications); patient-physician relationship; availability  
11 of family/social network support; and comorbidities (e.g. depression) amongst others<sup>6 7</sup>.  
12 A recent systematic review from RCTs on interventions to improve adherence to  
13 medications in patients with ASCVD has shown that there are several potential  
14 interventions, and, importantly, that simple interventions might be as effective as  
15 complex ones (and therefore easier to replicate)<sup>8</sup>. However, this review also highlighted  
16 many limitations in the current evidence such as risk of bias, small sample sizes and lack  
17 of studies in LMICs where most of the patients with ASCVD live. Among the most  
18 promising simple strategies to increase adherence this review singled out Short Message  
19 Services (SMS) interventions.  
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31 Mobile phones have become an “essential” instrument of daily-life worldwide, with  
32 around ~7 billion subscribers of whom 78% are based in LMICs<sup>9</sup>. This makes mobile  
33 phones an “ideal instrument” to deliver health behaviour change interventions to large  
34 numbers of people at low cost. Systematic reviews of RCTs using mHealth interventions  
35 confirm that SMS can be successful in changing behaviour, including smoking cessation  
36 and improved adherence to HIV medications<sup>10,11</sup>. Patient factors influencing adherence,  
37 such as knowledge attitudes and beliefs could be amenable to change using mobile  
38 phone messages sent to patients.  
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44 A recent Cochrane review evaluated the effects on adherence to medications of SMS in  
45 patients with ASCVD<sup>12</sup>. The review identified seven trials (1310 participants) and showed  
46 a beneficial effect of SMS on adherence to medication in six of them. However, the  
47 quality of the evidence was very low. Limitations identified by the Cochrane review were:  
48 (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-  
49 up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV)  
50 the majority of studies recruited only patients with acute coronary syndrome leaving out  
51 an important group of patients with other arterial occlusive events (e.g. ischemic stroke,  
52 peripheral vascular disease and programmed coronary revascularizations) that should  
53 be amenable for such type of intervention; (V) few studies were conducted in LMICs; and  
54 (VI) most trials did not describe the processes behind the SMS content generation, and  
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3 few that reported them did not target the key knowledge and attitudinal factors known to  
4 influence adherence to medication; instead interventions were simple “reminders”.

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

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

## 22 23 24 25 26 27 28 29 30 31 **METHODS AND ANALYSIS**

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33 This protocol is reported following the SPIRIT Standard Protocol Items recommendations  
34 for Interventional Trials<sup>13</sup>.

### 35 36 37 38 39 **Aim and objectives**

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

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

### 49 50 51 52 53 54 55 56 57 **Choice of comparator**

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

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19 Txt2 Heart Colombia is a two-parallel arm, only-blind individually randomized controlled  
20 trial. This design is aimed to minimize any potential bias that affects the internal validity  
21 of the study. The selection criteria have been designed to increase the number of  
22 potential beneficiaries of the intervention and to keep the selection process as close as  
23 possible to the future scenario in which the intervention will be implemented. Therefore,  
24 Txt2Heart-Colombia is pragmatic in design. The active intervention will be the SMS  
25 delivered by mobile phones and the content of the SMS is aimed to modified behaviour  
26 associated with poor adherence to ASCVDs medications in ASCVDs patients.  
27 Randomization will be performed as block randomization with a 1:1 allocation.  
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### 34 **Study setting**

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

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46 Inclusion criteria: Adult patients  $\geq 18$  years old with a history of at least one of the  
47 following arterial occlusive events: acute coronary syndrome (unstable angina, acute  
48 myocardial infarction with or without ST elevation), stable angina, ischemic  
49 cerebrovascular disease, peripheral arterial disease or coronary revascularization  
50 (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary  
51 angioplasty (PTCA). Patients should own a mobile phone and be able to read SMS.  
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55 Exclusion Criteria: Known contraindication to take all appropriate cardiovascular  
56 secondary prevention medications.  
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### 60 **Intervention**

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

### Outcomes

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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

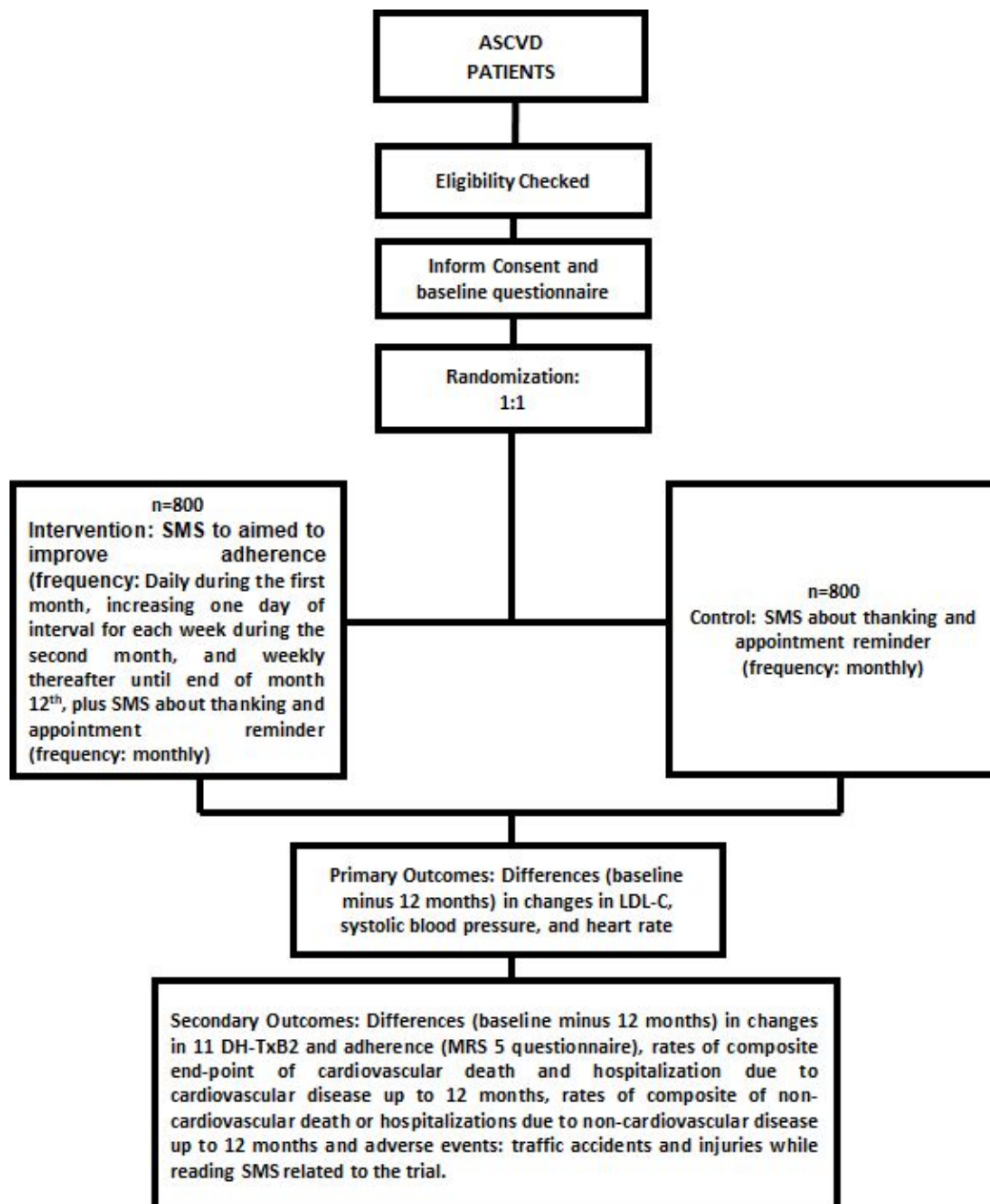
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3 hospitalizations due to non-cardiovascular disease. We will also include road traffic  
4 crashes (the only potential known hazard of text messaging) and death due to all causes  
5 as secondary outcomes.  
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###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

10 Participants who fulfil the eligibility criteria and provide their informed consent, will be  
11 recruited into the txt2heart trial. At first visit, after the participant has provided informed  
12 consent, baseline characteristics will be collected through questionnaires (MARS-5 and  
13 PHQ-9 Patient Health Questionnaire), blood samples, blood pressure, and heart rate.  
14 Participants will be then randomised to the intervention or control arm. The trial  
15 intervention will start the day after recruitment and will continue for 12 months to a  
16 maximum of 36 months, or when the participant withdraws from the study, or dies. Three  
17 months later, during the second visit, we will conduct a phone follow up interview to  
18 evaluate adequate SMS delivery and occurrence of clinical events. Finally, in the third  
19 visit (12 months later) we will collect data on adherence to cardiovascular medications  
20 (MARS-5), blood pressure, heart rate and clinical end-points. The 12 months follow up  
21 marks the primary outcome point. For patients with follow up beyond 12 months, we will  
22 have (by phone) assessment of clinical outcomes (death from cardiovascular causes  
23 and hospitalization due to nonfatal acute coronary syndrome, nonfatal stroke, or urgent  
24 revascularization) every 6 months until 36 months, the longest available follow-up.  
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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 mg/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 tx2heart trial will conduct a blinded assessment of



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2  
3 outcomes. Research personnel collecting data on clinical events, adherence scales, and  
4 biomarkers will not have access to treatment allocation. The laboratory results will be  
5 conducted once trial follow-up is completed. Are there going to be SOPs (Standard  
6 Operating Procedures) for measuring BP, heart rate? And are the bloods all going to be  
7 analysed in the same lab? Or different ones? Even if the same one, are there  
8 standardized procedures, and will there be some way of checking that changes over time  
9 are not simply due to measurement error?  
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### 15 16 **Data collection methods**

17 Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered  
18 in the CommCare platform, designed by Dimagi. CommCare is an open source mobile  
19 platform designed for data collection, client management, decision support, and  
20 behaviour change communication. The electronic devices (desktop computers, laptops  
21 and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by  
22 Fundación Cardiovascular de Colombia. Methods used to ensure high follow up  
23 achieved?  
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### 30 31 **Clinical outcomes**

32 Death from cardiovascular causes and hospitalization due to nonfatal acute coronary  
33 syndrome, nonfatal stroke, or urgent revascularization will be defined by local  
34 investigators based on clinical notes, and clear objective criteria using the suggestions  
35 provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular  
36 Endpoint Events in Clinical Trials<sup>17</sup>.  
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### 41 *Self-reported adherence*

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

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

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

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

### 55 **Protocol amends**

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57 Protocol trial has not been modified.  
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### **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.

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## Authors' contributions

## Study director

1  
2  
3 Norma Cecilia Serrano Díaz, MSc: Senior researcher and Research Department Director  
4 at Fundación Cardiovascular de Colombia. Dr Serrano participated in the choosing of  
5 the biomarkers and the processing design of biological samples.  
6  
7

8  
9 *Principal investigator*  
10

11  
12 Anderson Bermon Angarita, MSc: Junior researcher and epidemiologist at Fundación  
13 Cardiovascular de Colombia. Dr Bermon participated in the trial design and studied the  
14 impact of the results in Colombia, considering the healthcare system limitations.  
15  
16

17  
18 Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor  
19 Faculty of Psychology, Pontificia Bolivariana University. Dr Uribe designed the  
20 messages intervention and studied the behavioural theories that support the intervention  
21 methodology.  
22  
23  
24

25  
26 *Study chair*  
27

28  
29 Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University  
30 College London at Massachusetts Veterans Epidemiology Research and Information  
31 Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr Casas  
32 conceived the idea of conducting the trial and participated in methodology design of the  
33 trial  
34  
35  
36  
37

38  
39 Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology &  
40 Population Health London School of Hygiene & Tropical Medicine. Dr Perel conceived  
41 the idea of conducting and participated in methodology design of the trial  
42  
43  
44

45  
46 *Sub investigators:*  
47

48  
49 Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research  
50 Department of Primary Care and Population Health, University College London. Dr  
51 Murray contributed in the intervention design and messages validity process.  
52  
53  
54

55  
56 David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population  
57 Health London School of Hygiene & Tropical Medicine. Dr Prieto-Merino designed the  
58 statistical analysis and data management of the trial.  
59  
60

1  
2  
3 Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London  
4 School of Hygiene & Tropical Medicine. Dr Free conceived the idea of conducting and  
5 participated in the validity process of the messages intervention.  
6  
7

8  
9 Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr Atkins  
10 contributed in the messages intervention design.  
11  
12

13  
14 Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of  
15 Pharmacy, University College London. Dr Horne participated in the validity process of  
16 the messages intervention and the choosing of adherence scales.  
17  
18

19  
20 Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación  
21 Cardiovascular de Colombia. Dr Guio participated in the choosing of the biomarkers and  
22 the processing design of biological samples.  
23  
24

25  
26 Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at  
27 Cooperativa Colombia University. Dr Cáceres contributed in the trial design.  
28  
29

30  
31 Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant  
32 researcher at Pontificia Bolivariana University. As young researcher Psy. Pérez  
33 participated in the intervention design.  
34  
35

### 36 37 38 **Acknowledgements statement**

39  
40 We would like to thank to cardiology department medical staff at Fundación  
41 Cardiovascular de Colombia for their help with developing our research questions.  
42  
43

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48  
49 Fundación Cardiovascular de Colombia, Floridablanca

50  
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52 Reference MR/N021304/1  
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55 Universidad Pontificia Bolivariana, Bucaramanga sectional  
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3 **Competing interests statement**  
4

5 All authors declare there is not conflict of interest.  
6

7 All funding institutions declare there is not conflict of interest.  
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For peer review only

# 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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	2
2				
3	data set		Registration Data Set	
4				
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6	Protocol version	<a href="#">#3</a>	Date and version identifier	15
7				
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10	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
11				
12				
13	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	18
14				
15	responsibilities:			
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17	contributorship			
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20	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
21				
22	responsibilities:			
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24	sponsor contact			
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26	information			
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29				
30	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	18
31				
32	responsibilities:		collection, management, analysis, and interpretation of	
33				
34	sponsor and funder		data; writing of the report; and the decision to submit the	
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42	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	18
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44	responsibilities:		centre, steering committee, endpoint adjudication	
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46	committees		committee, data management team, and other individuals or	
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54	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
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56	rationale		undertaking the trial, including summary of relevant studies	
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1		(published and unpublished) examining benefits and harms	
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3		for each intervention	
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6	Background and	<a href="#">#6b</a> Explanation for choice of comparators	7
7			
8	rationale: choice of		
9			
10	comparators		
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13	Objectives	<a href="#">#7</a> Specific objectives or hypotheses	7
14			
15			
16	Trial design	<a href="#">#8</a> Description of trial design including type of trial (eg, parallel	7
17		group, crossover, factorial, single group), allocation ratio,	
18		and framework (eg, superiority, equivalence, non-inferiority,	
19		exploratory)	
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26	Study setting	<a href="#">#9</a> Description of study settings (eg, community clinic,	8
27		academic hospital) and list of countries where data will be	
28		collected. Reference to where list of study sites can be	
29		obtained	
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43	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If applicable,	8
44		eligibility criteria for study centres and individuals who will	
45		perform the interventions (eg, surgeons, psychotherapists)	
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51	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	8
52		replication, including how and when they will be	
53	description	administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	9
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	10
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13	adherence		and any procedures for monitoring adherence (eg, drug	
14			tablet return; laboratory tests)	
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19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	8
20				
21	concomitant care		permitted or prohibited during the trial	
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24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	13
25			specific measurement variable (eg, systolic blood pressure),	
26			analysis metric (eg, change from baseline, final value, time	
27			to event), method of aggregation (eg, median, proportion),	
28			and time point for each outcome. Explanation of the clinical	
29			relevance of chosen efficacy and harm outcomes is strongly	
30			recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	9
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly recommended	
44			(see Figure)	
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study	11
52			objectives and how it was determined, including clinical and	
53			statistical assumptions supporting any sample size	
54			calculations	
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	11
2			reach target sample size	
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6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	12
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a random	
9			sequence, details of any planned restriction (eg, blocking)	
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11			should be provided in a separate document that is	
12			unavailable to those who enrol participants or assign	
13			interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	12
24	concealment		central telephone; sequentially numbered, opaque, sealed	
25			envelopes), describing any steps to conceal the sequence	
26	mechanism		until interventions are assigned	
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	12
34	implementation		participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12
42			trial participants, care providers, outcome assessors, data	
43			analysts), and how	
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48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
51	unblinding			
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56	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	13
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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

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15	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-
16			
17	retention		up, including list of any outcome data to be collected for
18			participants who discontinue or deviate from intervention
19			protocols
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25	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including
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27			any related processes to promote data quality (eg, double
28			data entry; range checks for data values). Reference to
29			where details of data management procedures can be
30			found, if not in the protocol
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37	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
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39			outcomes. Reference to where other details of the statistical
40			analysis plan can be found, if not in the protocol
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44	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and
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46	analyses		adjusted analyses)
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50	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-
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52	population and		adherence (eg, as randomised analysis), and any statistical
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54	missing data		methods to handle missing data (eg, multiple imputation)
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57	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary
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1	formal committee	of its role and reporting structure; statement of whether it is	
2		independent from the sponsor and competing interests; and	
3		reference to where further details about its charter can be	
4		found, if not in the protocol. Alternatively, an explanation of	
5		why a DMC is not needed	
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12	Data monitoring:	<a href="#">#21b</a> Description of any interim analyses and stopping guidelines,	15
13	interim analysis	including who will have access to these interim results and	
14		make the final decision to terminate the trial	
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20	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing	17
21		solicited and spontaneously reported adverse events and	
22		other unintended effects of trial interventions or trial conduct	
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28	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any,	15
29		and whether the process will be independent from	
30		investigators and the sponsor	
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35	Research ethics	<a href="#">#24</a> Plans for seeking research ethics committee / institutional	15
36	approval	review board (REC / IRB) approval	
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41	Protocol	<a href="#">#25</a> Plans for communicating important protocol modifications	15
42	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
43		relevant parties (eg, investigators, REC / IRBs, trial	
44		participants, trial registries, journals, regulators)	
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51	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or assent from potential	16
52		trial participants or authorised surrogates, and how (see	
53		Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	16
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3	ancillary studies		participant data and biological specimens in ancillary	
4			studies, if applicable	
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8	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	16
9			participants will be collected, shared, and maintained in	
10			order to protect confidentiality before, during, and after the	
11			trial	
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18	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	16
19	interests		investigators for the overall trial and each study site	
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24	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	16
25			and disclosure of contractual agreements that limit such	
26			access for investigators	
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31	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	16
32	trial care		compensation to those who suffer harm from trial	
33			participation	
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39	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	17
40	trial results		results to participants, healthcare professionals, the public,	
41			and other relevant groups (eg, via publication, reporting in	
42			results databases, or other data sharing arrangements),	
43			including any publication restrictions	
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51	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	17
52	authorship		professional writers	
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57	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	17
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1	reproducible	participant-level dataset, and statistical code	
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3	research		
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6	Informed consent	<a href="#">#32</a> Model consent form and other related documentation given	16
7			
8	materials	to participants and authorised surrogates	
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11	Biological specimens	<a href="#">#33</a> Plans for collection, laboratory evaluation, and storage of	13
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13		biological specimens for genetic or molecular analysis in the	
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16		current trial and for future use in ancillary studies, if	
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18		applicable	
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22 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
23 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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

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Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

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

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26 **Keywords:** Cardiovascular diseases, Health behavior, Medications adherence,  
27 mHealth, text messaging  
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31 **Word count:** 5006  
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### 34 Abstract

35  
36 **Introduction:** Evidence demonstrated that anti-platelet therapy, ACE inhibitors/ARB,  
37 beta-blockers and statins are cost-effective in patients with atherosclerotic  
38 cardiovascular diseases (ASCVD) for reducing the risk of ASCVD events.  
39 Unfortunately, there is abundant evidence that adherence to these cardiovascular  
40 medications is far from ideal. A recent Cochrane review showed a beneficial effect of  
41 SMS interventions on adherence to medication in ASCVD patients.  
42

43  
44 **Methods and analysis:** The Txt2heart study is a pragmatic randomized single-blind  
45 controlled trial. The objective is to evaluate the efficacy and safety of an intervention  
46 with SMS messages delivered by mobile phones to improve adherence to  
47 cardiovascular medications in patients with ASCVD. The intervention consists of  
48 behavioural techniques delivered via SMS. The primary outcomes are blood serum  
49 LDL-C levels as an indicator of adherence to statins, systolic blood pressure as an  
50 indicator of adherence to blood-lowering therapies and heart rate as an indicator of  
51 adherence to beta-blockers. Secondary outcomes will include urine levels of 11  
52 dhTxB2, adherence to cardiovascular medications and rates of cardiovascular death or  
53 hospitalization due to cardiovascular disease. More information is available in the  
54 supplementary files, trial summary (table 1.)  
55

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

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3 evaluate whether SMS messages delivered through mobile telephones change the  
4 behaviour of Colombian patients who have suffered a cardiovascular event. Trial  
5 results will be presented to the local health authorities, and if the intervention is  
6 effective and safe, we hope this strategy will be implemented quickly because of its low  
7 cost and wide-reaching impact on the population.  
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12 **Trial registration number:** ClinicalTrials.gov: NCT03098186  
13

### 14 15 **Strengths and limitations of this study.** 16

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18  
19 This trial uses biomarkers to evaluate medication adherence.  
20

21 This trial uses an innovative intervention through SMS methodology based on  
22 behaviour theories.  
23

24 However, there is variability in the time of biomarkers. Therefore, we will use two  
25 additional measures to evaluate adherence.  
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## 28 29 **INTRODUCTION**

30 Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death  
31 worldwide. Approximately 35 million people worldwide have an acute coronary event or  
32 cerebrovascular event annually, and one quarter of these events occur in people with  
33 established ASCVD<sup>1</sup>. These arterial occlusive events occur at an early age in low and  
34 middle-income countries (LMICs), which affects economically active populations and  
35 resulting in large economic impacts<sup>2</sup>.  
36  
37

38 Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet  
39 therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing  
40 the risk of ASCVD events in patients with established ASCVD, and these agents are  
41 included in the list of the World Health Organization (WHO) Essential Medicines List  
42 (EML)<sup>3</sup>. Treatment with these four proven medications (together with smoking  
43 cessation) prevents or postpones approximately 75-80% of recurrent vascular events  
44 and their complications, such as death and disability<sup>4</sup>.  
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47 Unfortunately, there is abundant evidence that the worldwide adherence to these  
48 cardiovascular medications in patients with ASCVD is far from ideal. Less than half of  
49 patients with known ASCVD disease in high-income countries are receiving this group  
50 of cardiovascular medications, and the situation is much worse in LMICs. The PURE  
51 study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four  
52 types of cardiovascular drugs<sup>5</sup>.  
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3 A wide range of socio-economic and service level factors influence whether patients  
4 obtain medications, including the availability of medication (drugs out of stock), the lack  
5 of affordable medication and service factors, such as the availability and training of  
6 health care providers. Adherence to medication focuses on whether patients take the  
7 prescribed medication. Two recent systematic reviews on patient factors that affect  
8 adherence to ASCVD medications in secondary prevention showed that these factors  
9 go far beyond simply “forgetting” to take the medication and include a range of factors,  
10 including patients’ perceptions of the cause and prognosis of the illness (e.g., fatalistic  
11 perceptions or absence of symptoms) and/or the risks and benefits of medications  
12 (e.g., fear of side effects or concern about multiple medications), the patient-physician  
13 relationship, availability of family/social network support, and comorbidities (e.g.,  
14 depression)<sup>6 7</sup>.

15  
16 A recent systematic review from RCTs on interventions to improve adherence to  
17 medications in patients with ASCVD demonstrated several potential interventions, and  
18 importantly, simple interventions may be as effective as complex ones (and therefore  
19 easier to replicate)<sup>8</sup>. However, this review also highlighted many limitations in the  
20 current evidence, such as risk of bias, small sample sizes and lack of studies in LMICs,  
21 where most of the patients with ASCVD live. Among the most promising simple  
22 strategies to increase adherence, this review singled out Short Message Service (SMS)  
23 interventions.

24  
25 Mobile phones have become an “essential” instrument of daily life worldwide, with  
26 approximately 7 billion subscribers, of whom 78% are based in LMICs<sup>9</sup>. This use  
27 makes mobile phones an “ideal instrument” to deliver health behaviour change  
28 interventions to large numbers of people at a low cost. Systematic reviews of RCTs  
29 using mHealth interventions confirm that SMS can be successful in changing  
30 behaviour, including smoking cessation and improved adherence to HIV  
31 medications<sup>10,11</sup>. Patient factors influencing adherence, such as knowledge attitudes  
32 and beliefs, could be amenable to change using mobile phone messages sent to  
33 patients.

34  
35 A recent Cochrane review evaluated the effects of SMS on adherence to medications  
36 in patients with ASCVD<sup>12</sup>. The review identified seven trials (1310 participants) and  
37 showed a beneficial effect of SMS on adherence to medications in six of these trials.  
38 However, the quality of the evidence was very low. The Cochrane review identified the  
39 following limitations: (I) trials of small sample size (34 to 521 participants); (II) most  
40 trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited  
41 clinical relevance; (IV) most studies recruited only patients with acute coronary  
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3 syndrome, which leaves out an important group of patients with other arterial occlusive  
4 events (e.g., ischaemic stroke, peripheral vascular disease and programmed coronary  
5 revascularizations) who should be amenable for this type of intervention; (V) few  
6 studies were performed in LMICs; and (VI) most trials did not describe the processes  
7 behind the SMS content generation, and the few trials that did report these processes  
8 did not target the key knowledge and attitudinal factors that are known to influence  
9 adherence to medication; instead the interventions were simple “reminders”.

10  
11 In conclusion, given the high prevalence of people with ASCVD in LMICs and the low  
12 use of cost-effective secondary prevention medications, a low-cost intervention that  
13 builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential  
14 to improve public health. The current evidence shows that SMS interventions based on  
15 behaviour-change techniques are a potentially effective strategy to increase adherence  
16 to medications in people with ASCVD. However, further large trials are needed.

17  
18 To provide the high-quality evidence needed to assess the effect of SMS interventions  
19 based on behaviour-change techniques to increase adherence to medications in  
20 patients with ASCVD, we designed the txt2heart study, which is a large pragmatic  
21 superiority parallel randomized single-blind controlled trial with a 1:1 allocation ratio to  
22 evaluate the efficacy and safety of SMS on adherence to cardiovascular medications.  
23 The trial is being performed in a setting (Colombia) where patient factors, such as  
24 knowledge, attitudes and beliefs, are important determinants of adherence. In this  
25 context, medicines are widely available and generally affordable, so an intervention  
26 delivered to patients via SMS has the potential to be effective.

## 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

### **METHODS AND ANALYSIS**

This protocol is reported following the SPIRIT Standard Protocol Items  
recommendations for Interventional Trials<sup>13</sup>.

#### **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

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3 an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and  
4 heart rate as an indicator of adherence to beta-blockers.  
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8 The secondary objective is to assess the impact of mobile text messaging on  
9 adherence to medications, hospitalizations, and the composite end-point of incident  
10 Major Adverse Cardiovascular Events (MACE) at 12 months.  
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### 13 14 **Choice of comparator**

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

34 Txt2heart Colombia is a two-parallel arm, single-blind individually randomized  
35 controlled trial. This design is aimed to minimize any potential bias that affects the  
36 internal validity of the study. The selection criteria were designed to increase the  
37 number of potential beneficiaries of the intervention and to keep the selection process  
38 as close as possible to the future scenario in which the intervention will be  
39 implemented. Therefore, Txt2Heart-Colombia is pragmatic in design. The active  
40 intervention will be the SMS delivered to mobile phones, and the content of the SMS is  
41 aimed to modify behaviours associated with poor adherence to ASCVD medications in  
42 ASCVD patients. Randomization will be performed as block randomization with a 1:1  
43 allocation.  
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### 52 **Study setting**

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

Inclusion criteria: Adult patients  $\geq 18$  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<sup>14</sup>. 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<sup>15</sup>. 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<sup>16</sup>. 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

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3 be a one-way intervention. Due to a lack of economic resources, we will not tailor the  
4 messages. The trial intervention will start the day after recruitment and continue for 12  
5 months or until the participant withdraws from the study or dies. The follow-up duration  
6 will be at least 12 months to a maximum of 36 months. Participants will not receive  
7 messages after month 12.  
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### 11 12 **Outcomes**

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14 The primary outcomes were selected for their clinical relevance and differences in  
15 changes (12 months “minus” baseline) in *Blood serum LDL-C levels* as an indicator of  
16 adherence to statins, *systolic blood pressure* as an indicator of adherence to blood-  
17 lowering therapies (ACE inhibitors or ARBs) and *heart rate* as an indicator of  
18 adherence to beta-blockers.  
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23 The following secondary outcomes will be included: *Urine levels of 11 dhTxB2* as an  
24 indicator of adherence to antiplatelet therapy; *adherence to cardiovascular medications*  
25 used in secondary prevention as measured using the MARS-5 questionnaire; and rates  
26 of cardiovascular death or hospitalization due to cardiovascular disease and non-  
27 cardiovascular death or hospitalizations due to non-cardiovascular disease. We will  
28 also include road traffic crashes (the only potential known hazard of text messaging)  
29 and death due to all causes as secondary outcomes.  
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### 36 **Participant timeline**

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

	52.4						
	%	2.36	0.47	1.89	77%	97%	100%
Atorvastatin 40							
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

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

11  
12 Blinding: Because of the nature of the intervention (SMS messages), it is not possible  
13 to include blind participants. However, the tx2heart trial will perform a blinded  
14 assessment of outcomes. Research personnel collecting data on clinical events,  
15 adherence scales, and biomarkers will not have access to treatment allocation. The  
16 laboratory results will be performed once trial follow-up is completed.

### 25 **Data collection methods**

26  
27 Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be  
28 entered in the CommCare platform, designed by Dimagi. CommCare is an open source  
29 mobile platform designed for data collection, client management, decision support, and  
30 behaviour change communication. The electronic devices (desktop computers, laptops  
31 and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by  
32 Fundación Cardiovascular de Colombia.

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

### 59 **Clinical outcomes**

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3 Death from cardiovascular causes and hospitalization due to nonfatal acute coronary  
4 syndrome, nonfatal stroke, or urgent revascularization will be defined by local  
5 investigators based on clinical notes and clear objective criteria using the suggestions  
6 provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular  
7 Endpoint Events in Clinical Trials<sup>17</sup>.  
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### 11 *Self-reported adherence*

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

34 Physiological measurements of heart rate and blood pressure will be measured using a  
35 calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by  
36 trained health care professionals. Patients will sit quietly for 10 minutes before the  
37 examinations.  
38

39 Blood LDL-C: Quantification of serum LDL will be performed using automated  
40 equipment by a direct method.  
41

42 Recent large epidemiological studies confirmed that resting heart rate is an  
43 independent predictor of cardiovascular mortality. Heart rate decrease is itself an  
44 important mechanism of the benefit of the blockers and other drugs that reduce heart  
45 rate after an acute myocardial infarction (1–4). Controversies on the optimal dose to  
46 obtain results remain, but the reduction in heart rate is notorious in patients receiving  
47 beta-blockers (5). In Colombia, beta-blockers are a first-line drug used for secondary  
48 prevention. The most frequently beta-blocker is carvedilol, which exhibits advantages in  
49 decreasing heart rate and mortality in patients with some type of cardiovascular event  
50 (6).  
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### **Data management**



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

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

45 Data monitoring will be executed according to GCP Guidelines. This trial is a large,  
46 pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change  
47 behaviour and increase adherence of safe and proven effective interventions for  
48 secondary prevention that have been in clinical use for decades. Clinical management  
49 for underlying conditions will remain as per hospital's standard protocol. Based on  
50 these factors, the probability of harm or injury (physical, psychological, social or  
51 economic) occurring because of participation in this research study was assessed as  
52 low risk to participants in each of these categories. Based on the low risks associated  
53 with this trial, there will not be a data monitoring committee. However, a monitoring  
54 plan to ensure appropriate performance of the trial will be developed, which will  
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3 incorporate 100% central monitoring in conjunction with procedures, such as  
4 investigator training and meetings and written guidance. All data will be subject to  
5 statistical monitoring, and at least 10% of data will be subjected to on-site monitoring.  
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7 Investigators/institutions are required to provide direct access to source  
8 data/documents for trial-related monitoring, audits, ethics committee review and  
9 regulatory inspection. All trial-related and source documents must be kept for 15 years  
10 after the end of the trial.  
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### 15 **Indirect Patient and Public Involvement**

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

### 27 **Protocol amendments**

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29 The protocol for the trial has not been modified.  
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### 33 **Ethical considerations**

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35 The study will be performed in compliance with the protocol, regulatory requirements,  
36 GCP and the ethical principles of the Declaration of Helsinki.  
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### 40 **Ethical approval**

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42 The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and  
43 approved the trial.  
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### 46 **Informed Consent:**

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48 The investigator or designated personnel will inform the patient of the objectives,  
49 methods, anticipated benefits and potential risks and inconveniences of the study. The  
50 patient will be given every opportunity to clarify any points he/she does not understand  
51 and, if necessary, ask for more information. Written consent must be given by the  
52 patient and/or the legal guardian of the patient after detailed information about the  
53 study is provided in accordance with any national provisions on the protection of clinical  
54 study patients. The verbal explanation will cover all of the elements specified in the  
55 written information provided to the patient. Patients and/or legal guardians will be  
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3 required to sign and date the informed consent form. Patients who refuse to give or  
4 who withdraw written informed consent will not be included or continue in the study.  
5 The trial will include a "Pre-selection" Informed Consent, per law 1581 of 2012 and  
6 decree 1377 of 2013 or law of protection of personal data, where the study team is  
7 authorized to handle personal and clinical data of the subject. Calls made in the pre-  
8 selection and phase 2 visit will be recorded and stored for a set time. Eligible  
9 participants will only be included in the study after signing "Txt2Heart-Colombia"  
10 informed consent (testified, where required by law or regulation), as approved by the  
11 ethics committees. The process will be documented in the patient source documents,  
12 specifically in CRFs (Case Report Form).  
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20 Confidentiality: Information about the study subjects will be kept confidential. The  
21 investigators will ensure the anonymity of patients, and patients will not be identified by  
22 name in any document. Informed consent forms and patient recruitment registration will  
23 be kept strictly confidential only to permit identification of the patient at Fundación  
24 Cardiovascular de Colombia. Information about the study subjects will be handled  
25 under the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of  
26 2013, Law of data protection). The regulations that require an authorization signed by  
27 the patient including the follow information: What protected health information (PHI) will  
28 be collected from the study subjects, who will have access to that information and why,  
29 who will use and disclose that information and the right to withdraw his/her  
30 authorization to use their PHI.  
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#### 40 **Access to data**

41 The principal investigator and sub-investigators will have access to the data to verify  
42 and analyse the results. To ensure confidentiality, all of the investigators will be blinded  
43 of participant identification.  
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#### 47 **Ancillary and post-trial care**

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50 Due to its low risk, the intervention in this trial will not include insurance for participants.  
51 However, we will refer patients to their medical services in case we think that they need  
52 assistance. Furthermore, a full explanation of the scope and limitations of the study will  
53 be told to the patients before they sign the informed consent.  
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#### 58 **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.

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## 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*

1  
2  
3 Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University  
4 College London at Massachusetts Veterans Epidemiology Research and Information  
5 Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas  
6 conceived the idea of conducting the trial and participated in the methodology design of  
7 the trial.  
8  
9

10  
11  
12 Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology &  
13 Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived  
14 the idea of conducting the trial and participated in the methodology design of the trial.  
15  
16

17  
18  
19 *Sub-investigators:*

20  
21  
22 Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research  
23 Department of Primary Care and Population Health, University College London. Dr.  
24 Murray contributed in the intervention design and message validity process.  
25  
26

27  
28 David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population  
29 Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the  
30 statistical analysis and data management of the trial.  
31  
32

33  
34 Caroline Free: Associate Professor Faculty of Epidemiology & Population Health  
35 London School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of  
36 conducting and participated in the validity process of the message intervention.  
37  
38

39  
40 Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins  
41 contributed in the message intervention design.  
42  
43

44  
45 Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of  
46 Pharmacy, University College London. Dr. Horne participated in the validity process of  
47 the message intervention and choosing adherence scales.  
48  
49

50  
51 Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación  
52 Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the  
53 processing design for biological samples.  
54  
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56  
57  
58 Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at  
59 Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.  
60

1  
2  
3  
4 Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant  
5 researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez  
6 participated in the intervention design.  
7  
8  
9

### 10 11 **Acknowledgments statement** 12

13 We thank the Cardiology Department medical staff at Fundación Cardiovascular de  
14 Colombia for their help with developing our research questions.  
15  
16

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21

22 Fundación Cardiovascular de Colombia, Floridablanca  
23

24 London School of Hygiene and Tropical Medicine, UK Medical Research Council  
25

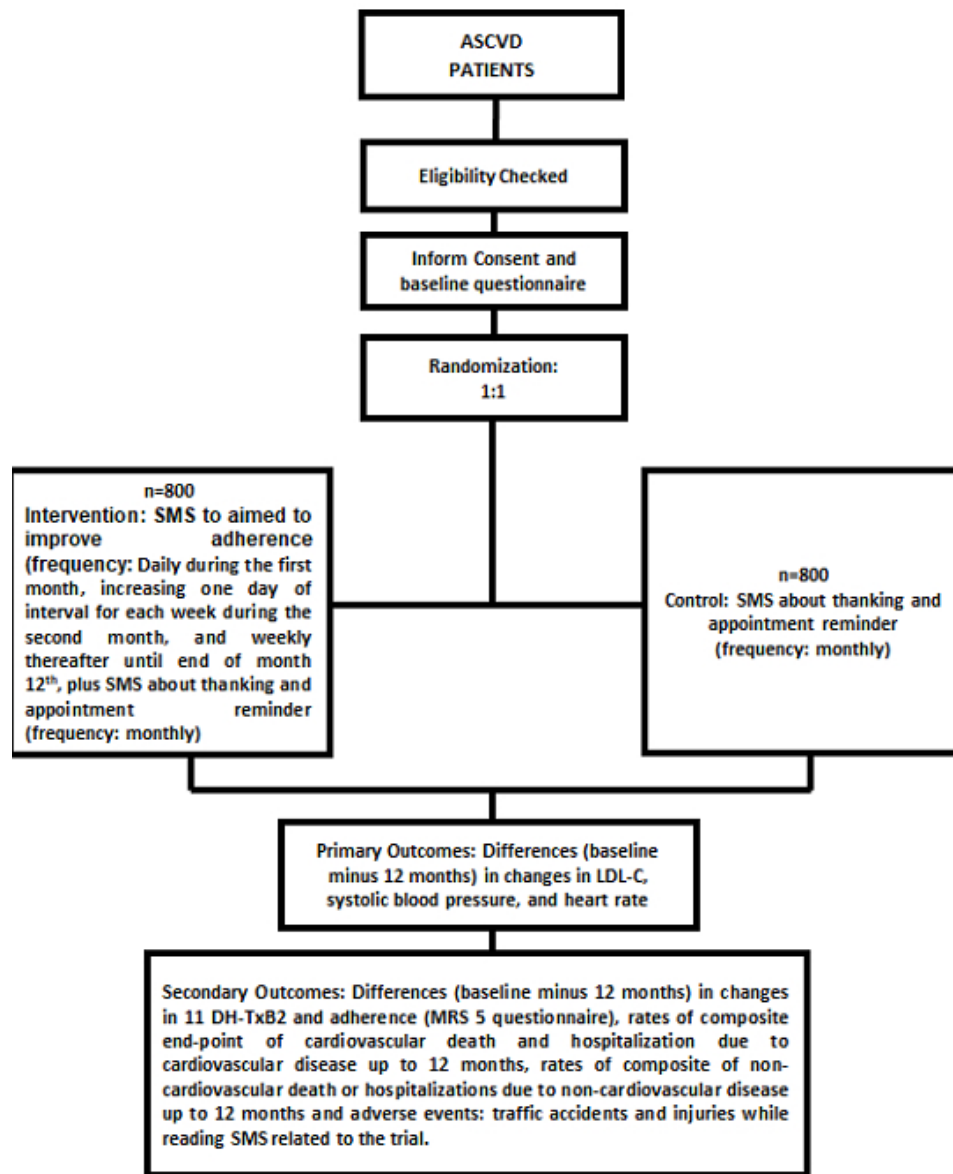
26 Funded Reference MR/N021304/1  
27

28 Universidad Pontificia Bolivariana, Bucaramanga sectional  
29  
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### 31 **Competing interests' statement** 32

33 All authors declare there is not conflict of interest.  
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35 All funding institutions declare there is not conflict of interest.  
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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: <a href="mailto:contacto@colciencias.gov.co">contacto@colciencias.gov.co</a> (+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	<p>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.</p> <p>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.</p>
Key inclusion and exclusion criteria	<p>Inclusion Criteria:</p> <p>Age <math>\geq 18</math> years old</p> <p>Sexes eligible for study: both</p> <p>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,</p> <p>peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).</p> <p>Own at least one mobile phone</p>

	<p>Ability to read and understand text messages (SMS)</p> <p>Intention to stay in the country of recruitment during the next 12 months</p> <p>Exclusion Criteria:</p> <p>Contraindication to take all cardiovascular medications used in secondary prevention.</p> <p>Participation in another randomized clinical trial that could interfere with adherence to treatment.</p>
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)	<p>Differences in changes (baseline minus 12 months) of:</p> <p>Low density lipoprotein cholesterol (LDL-C)</p> <p>Systolic Blood pressure</p> <p>Heart Rate</p>
Key secondary outcomes	<p>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.</p> <p>Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months.</p> <p>Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months</p> <p>Adverse events: traffic accidents and injuries while reading SMS related to the trial.</p>

# 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:

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

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	2
2				
3	data set		Registration Data Set	
4				
5				
6	Protocol version	<a href="#">#3</a>	Date and version identifier	15
7				
8				
9				
10	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
11				
12				
13	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	18
14				
15	responsibilities:			
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17	contributorship			
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20	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
21				
22	responsibilities:			
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24	sponsor contact			
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26	information			
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30	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	18
31				
32	responsibilities:		collection, management, analysis, and interpretation of	
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34	sponsor and funder		data; writing of the report; and the decision to submit the	
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42	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	18
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44	responsibilities:		centre, steering committee, endpoint adjudication	
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46	committees		committee, data management team, and other individuals or	
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54	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
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56	rationale		undertaking the trial, including summary of relevant studies	
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1		(published and unpublished) examining benefits and harms	
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3		for each intervention	
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6	Background and	<a href="#">#6b</a> Explanation for choice of comparators	7
7			
8	rationale: choice of		
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10	comparators		
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13	Objectives	<a href="#">#7</a> Specific objectives or hypotheses	7
14			
15			
16	Trial design	<a href="#">#8</a> Description of trial design including type of trial (eg, parallel	7
17		group, crossover, factorial, single group), allocation ratio,	
18		and framework (eg, superiority, equivalence, non-inferiority,	
19		exploratory)	
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25			
26	Study setting	<a href="#">#9</a> Description of study settings (eg, community clinic,	8
27		academic hospital) and list of countries where data will be	
28		collected. Reference to where list of study sites can be	
29		obtained	
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43	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If applicable,	8
44		eligibility criteria for study centres and individuals who will	
45		perform the interventions (eg, surgeons, psychotherapists)	
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51	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	8
52		replication, including how and when they will be	
53	description	administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	9
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	10
12				
13	adherence		and any procedures for monitoring adherence (eg, drug	
14			tablet return; laboratory tests)	
15				
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18				
19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	8
20				
21	concomitant care		permitted or prohibited during the trial	
22				
23				
24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	13
25			specific measurement variable (eg, systolic blood pressure),	
26			analysis metric (eg, change from baseline, final value, time	
27			to event), method of aggregation (eg, median, proportion),	
28			and time point for each outcome. Explanation of the clinical	
29			relevance of chosen efficacy and harm outcomes is strongly	
30			recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	9
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly recommended	
44			(see Figure)	
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study	11
52			objectives and how it was determined, including clinical and	
53			statistical assumptions supporting any sample size	
54			calculations	
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	11
2			reach target sample size	
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6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	12
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a random	
9			sequence, details of any planned restriction (eg, blocking)	
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11			should be provided in a separate document that is	
12			unavailable to those who enrol participants or assign	
13			interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	12
24	concealment		central telephone; sequentially numbered, opaque, sealed	
25	mechanism		envelopes), describing any steps to conceal the sequence	
26			until interventions are assigned	
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	12
34	implementation		participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12
42			trial participants, care providers, outcome assessors, data	
43			analysts), and how	
44				
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46				
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48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12
49	emergency		permissible, and procedure for revealing a participant's	
50	unblinding		allocated intervention during the trial	
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56	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	13
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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

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15	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow- 13
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17	retention		up, including list of any outcome data to be collected for
18			participants who discontinue or deviate from intervention
19			protocols
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25	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including 14
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27			any related processes to promote data quality (eg, double
28			data entry; range checks for data values). Reference to
29			where details of data management procedures can be
30			found, if not in the protocol
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37	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary 14
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39			outcomes. Reference to where other details of the statistical
40			analysis plan can be found, if not in the protocol
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45	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and 14
46			
47	analyses		adjusted analyses)
48			
49			
50	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non- 14
51			
52	population and		adherence (eg, as randomised analysis), and any statistical
53			methods to handle missing data (eg, multiple imputation)
54	missing data		
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58	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary 15
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1	formal committee		of its role and reporting structure; statement of whether it is	
2			independent from the sponsor and competing interests; and	
3			reference to where further details about its charter can be	
4			found, if not in the protocol. Alternatively, an explanation of	
5			why a DMC is not needed	
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12	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	15
13	interim analysis		including who will have access to these interim results and	
14			make the final decision to terminate the trial	
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20	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	17
21			solicited and spontaneously reported adverse events and	
22			other unintended effects of trial interventions or trial conduct	
23				
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28	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any,	15
29			and whether the process will be independent from	
30			investigators and the sponsor	
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35	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional	15
36	approval		review board (REC / IRB) approval	
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41	Protocol	<a href="#">#25</a>	Plans for communicating important protocol modifications	15
42	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
43			relevant parties (eg, investigators, REC / IRBs, trial	
44			participants, trial registries, journals, regulators)	
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51	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential	16
52			trial participants or authorised surrogates, and how (see	
53			Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	16
2				
3	ancillary studies		participant data and biological specimens in ancillary	
4			studies, if applicable	
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8	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	16
9			participants will be collected, shared, and maintained in	
10			order to protect confidentiality before, during, and after the	
11			trial	
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18	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	16
19	interests		investigators for the overall trial and each study site	
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24	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	16
25			and disclosure of contractual agreements that limit such	
26			access for investigators	
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31	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	16
32	trial care		compensation to those who suffer harm from trial	
33			participation	
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39	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	17
40	trial results		results to participants, healthcare professionals, the public,	
41			and other relevant groups (eg, via publication, reporting in	
42			results databases, or other data sharing arrangements),	
43			including any publication restrictions	
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51	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	17
52	authorship		professional writers	
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57	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	17
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1	reproducible	participant-level dataset, and statistical code	
2			
3	research		
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6	Informed consent	<a href="#">#32</a> Model consent form and other related documentation given	16
7			
8	materials	to participants and authorised surrogates	
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11	Biological specimens	<a href="#">#33</a> Plans for collection, laboratory evaluation, and storage of	13
12			
13		biological specimens for genetic or molecular analysis in the	
14			
15			
16		current trial and for future use in ancillary studies, if	
17			
18		applicable	
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22 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
23 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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

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<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

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3 **Evaluation of the efficacy and safety of text messages targeting adherence to**  
4 **cardiovascular medications in secondary prevention: The Txt2heart-Colombia**  
5 **randomized controlled trial protocol**  
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26 **Keywords:** Cardiovascular diseases, Health behavior, Medications adherence,  
27 mHealth, text messaging  
28  
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30  
31 **Word count:** 5006  
32  
33

### 34 **Abstract**

35  
36 **Introduction:** Anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are  
37 cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for  
38 reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that  
39 adherence to these cardiovascular medications is far from ideal. A recent Cochrane  
40 review showed a potential beneficial effect of SMS interventions on adherence to  
41 medication in ASCVD patients.  
42

43 **Methods and analysis:** The Txt2heart study is a pragmatic randomized single-blind  
44 controlled trial. The objective is to evaluate the efficacy and safety of an intervention with  
45 SMS messages delivered by mobile phones to improve adherence to cardiovascular  
46 medications in patients with ASCVD. The intervention consists of behavioural techniques  
47 delivered via SMS. The primary outcomes are changes in blood serum low-density  
48 lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins, systolic  
49 blood pressure as an indicator of adherence to blood-lowering therapies and heart rate  
50 as an indicator of adherence to beta-blockers. Secondary outcomes will include urine  
51 levels of 11-dehydrothromboxane B<sub>2</sub> (11dhTxB<sub>2</sub>), self-reported adherence to  
52 cardiovascular medications and rates of cardiovascular death or hospitalization due to  
53 cardiovascular disease.  
54  
55

56 **Ethics and dissemination:** The study will be performed in compliance with the protocol,  
57 regulatory requirements, Good Clinical Practice and ethical principles of the Declaration  
58 of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated  
59 and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to  
60



1  
2  
3 evaluate whether SMS messages delivered through mobile telephones change the  
4 behaviour of Colombian patients who have suffered a cardiovascular event. Trial results  
5 will be presented to the local health authorities, and if the intervention is effective and  
6 safe, we hope this strategy will be implemented quickly because of its low cost and wide-  
7 reaching impact on the population.  
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11 **Trial registration number:** ClinicalTrials.gov: NCT03098186  
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### 14 15 **Strengths and limitations of this study.** 16

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19 The trial uses an innovative intervention through SMS methodology based on behaviour  
20 theories.  
21

22 The trial uses biomarkers to evaluate medication adherence.  
23

24 The trial is the largest evaluating SMS to increase adherence for cardiovascular  
25 secondary prevention  
26

27 Measuring adherence is challenging; we are triangulating data from biomarkers and self-  
28 reported adherence to improve the accuracy of the trial measure of effect  
29  
30

### 31 **INTRODUCTION** 32

33 Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death  
34 worldwide. Approximately 35 million people worldwide have an acute coronary event or  
35 cerebrovascular event annually, and one quarter of these events occur in people with  
36 established ASCVD<sup>1</sup>. These arterial occlusive events occur at an early age in low and  
37 middle-income countries (LMICs), which affects economically active populations and  
38 results in large economic impacts<sup>2</sup>.  
39

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42 Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet  
43 therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the  
44 risk of ASCVD events in patients with established ASCVD, and these agents are included  
45 in the list of the World Health Organization (WHO) Essential Medicines List (EML)<sup>3</sup>.  
46 Treatment with these four proven medications (together with smoking cessation)  
47 prevents or postpones approximately 75-80% of recurrent vascular events and their  
48 complications, such as death and disability<sup>4</sup>.  
49

50  
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52 Unfortunately, there is abundant evidence that the worldwide adherence to these  
53 cardiovascular medications in patients with ASCVD is far from ideal. Less than half of  
54 patients with known ASCVD disease in high-income countries are receiving this group  
55 of cardiovascular medications, and the situation is much worse in LMICs. The PURE  
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3 study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types  
4 of cardiovascular drugs<sup>5</sup>.

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

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

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

51 A recent Cochrane review evaluated the effects of SMS on adherence to medications in  
52 patients with ASCVD<sup>12</sup>. The review identified seven trials (1310 participants) and showed  
53 a beneficial effect of SMS on adherence to medications in six of these trials. However,  
54 the quality of the evidence was very low. The Cochrane review identified the following  
55 limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a  
56 short follow-up (<6 months); (III) primary outcomes reported were of limited clinical  
57 relevance; (IV) most studies recruited only patients with acute coronary syndrome, which  
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3 leaves out an important group of patients with other arterial occlusive events (e.g.,  
4 ischaemic stroke, peripheral vascular disease and programmed coronary  
5 revascularizations) who should be amenable for this type of intervention; (V) few studies  
6 were performed in LMICs; and (VI) most trials did not describe the processes behind the  
7 SMS content generation, and the few trials that did report these processes did not target  
8 the key knowledge and attitudinal factors that are known to influence adherence to  
9 medication; instead the interventions were simple “reminders”.

10  
11 In conclusion, given the high prevalence of people with ASCVD in LMICs and the low  
12 use of cost-effective secondary prevention medications, a low-cost intervention that  
13 builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to  
14 improve public health. The current evidence shows that SMS interventions based on  
15 behaviour-change techniques are a potentially effective strategy to increase adherence  
16 to medications in people with ASCVD. However, further large trials are needed.

17  
18 To provide the high-quality evidence needed to assess the effect of SMS interventions  
19 based on behaviour-change techniques to increase adherence to medications in patients  
20 with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority  
21 parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the  
22 efficacy and safety of SMS on adherence to cardiovascular medications. The trial is  
23 being performed in a setting (Colombia) where patient factors, such as knowledge,  
24 attitudes and beliefs, are important determinants of adherence. In this context, medicines  
25 are widely available and generally affordable, so an intervention delivered to patients via  
26 SMS has the potential to be effective.

## 37 38 39 **METHODS AND ANALYSIS**

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41  
42 This protocol is reported following the SPIRIT Standard Protocol Items recommendations  
43 for Interventional Trials<sup>13</sup> (see supplementary file 1).

### 44 45 46 **Aim and objectives**

47  
48 The primary objective is to evaluate the efficacy and safety of an intervention with  
49 SMS messages delivered by mobiles phones to improve adherence to  
50 cardiovascular medications in patients with atherosclerotic cardiovascular disease  
51 (ASCVD). We will assess the intervention efficacy via the measurement of blood  
52 serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as  
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3 an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart  
4 rate as an indicator of adherence to beta-blockers.  
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8 The secondary objective is to assess the impact of mobile text messaging on self-  
9 reported adherence to medications, hospitalizations, and the composite end-point of  
10 incident Major Adverse Cardiovascular Events (MACE) at 12 months.  
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### 13 14 **Choice of comparator**

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

34 Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled  
35 trial. This design is aimed to minimize any potential bias that affects the internal validity  
36 of the study. The selection criteria were designed to increase the number of potential  
37 beneficiaries of the intervention and to keep the selection process as close as possible  
38 to the future scenario in which the intervention will be implemented. Therefore,  
39 Txt2Heart-Colombia is pragmatic in design. The active intervention will be the SMS  
40 delivered to mobile phones, and the content of the SMS is aimed to modify behaviours  
41 associated with poor adherence to ASCVD medications in ASCVD patients.  
42 Randomization will be performed as block randomization with a 1:1 allocation.  
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### 50 **Study setting**

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

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

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12 Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular  
13 secondary prevention medications.  
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### 16 17 **Intervention**

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19 The intervention under evaluation consists of *behavioural change techniques* (BCTs)  
20 delivered via SMS. We developed our intervention following the recommendations of  
21 Abroms et al<sup>14</sup>. First, we reviewed the literature on individual level factors that influence  
22 adherence to medication. We performed country-specific qualitative studies using focus  
23 group discussions and semi-structured interviews to evaluate cardiovascular patients'  
24 perceptions about mHealth programmes to determine the necessary content and  
25 preferred timing and frequency of the SMS messages. To construct the content of the  
26 SMS, we wrote messages using educational and enabling behaviour change functions  
27 and established BCTs to target the potentially modifiable factors that influence the  
28 adherence referred to in the literature and found in our qualitative studies<sup>15</sup>. Finally, we  
29 tested the SMS messages with participants and adapted the messages based on their  
30 feedback to ensure the messages were understandable, acceptable, and relevant<sup>16</sup>. The  
31 resultant intervention delivered by SMS provides information about health consequences  
32 of adherence or non-adherence, instruction on how to take medication, medicine-taking  
33 prompts and cues, support in establishing medicine-taking habits, reframing medicine-  
34 taking and provides or encourages social support for taking medication<sup>17</sup>. The messages  
35 were designed according to the Transtheoretical Model (TTM) (Prochaska &  
36 DiClemente, 1992) and were aimed to enhance actions related to the steps and  
37 processes of this model. We will send messages daily the first month, three times per  
38 week the second month and once weekly the last ten months. This reducing frequency  
39 is consistent with the TTM, which suggests that people in the early stages of change  
40 require more intense input than people in later stages. In accordance with data from the  
41 focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The  
42 intervention will be delivered through an electronic platform, and it will be a one-way  
43 intervention. We will explain patients that they should not answer the messages but they  
44 will be able to request to stop receiving the messages and withdraw from the trial by  
45 sending a message with the word "STOP". We will explain to patients that they should  
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3 send the 'stop' message in this situation . Stop messages will be saved and monitored  
4 by a trained engineer, separate from the study team, in order to maintain blinding.  
5 Similarly, a trained engineer, separate from the study team, will save and monitor the  
6 patients' answers if they respond to the messages. Because of the pragmatic nature of  
7 our study we will not tailor the messages. The trial intervention will start the day after  
8 recruitment and continue for 12 months or until the participant withdraws from the study  
9 or dies. The follow-up duration will be at least 12 months to a maximum of 36 months.  
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14 Participants will not receive messages after month 12.  
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### 17 **Outcomes**

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19 The primary outcomes were selected for their clinical relevance and include: differences  
20 in changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of  
21 adherence to statins, *systolic blood pressure* as an indicator of adherence to blood-  
22 lowering therapies (ACE inhibitors or ARBs) and *heart rate* as an indicator of adherence  
23 to beta-blockers.  
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28 The following secondary outcomes will be included: *Urine levels of 11 dhTxB2* as an  
29 indicator of adherence to antiplatelet therapy; *self-reported adherence to cardiovascular*  
30 *medications* used in secondary prevention as measured using the MARS-5  
31 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular  
32 disease and non-cardiovascular death or hospitalizations due to non-cardiovascular  
33 disease. We will also include road traffic crashes (the only potential known hazard of text  
34 messaging) and death due to all causes as secondary outcomes.  
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### 41 **Participant timeline**

42 Participants who fulfil the eligibility criteria and provide their informed consent will be  
43 recruited into the txt2heart trial. After the participant provided informed consent, baseline  
44 characteristics will be collected at the first visit using questionnaires (MARS-5 and PHQ-9  
45 Patient Health Questionnaire), blood samples, blood pressure, and heart rate.  
46  
47 Participants will be randomized to the intervention or control arm. The trial intervention  
48 will start the day after recruitment and will continue for 12 months to a maximum of 36  
49 months, or when the participant withdraws from the study, or dies. We will perform a  
50 phone follow-up interview three months later, during the second visit, to evaluate  
51 adequate SMS delivery and the occurrence of clinical events. Finally, we will collect data  
52 on self-reported adherence to cardiovascular medications (MARS-5), blood pressure,  
53 heart rate and clinical end-points in the third visit (12 months later). The 12-month follow  
54 up marks the primary outcome point. For patients with follow up beyond 12 months, we  
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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



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3 Randomization: We will use block randomization (varying size), stratifying by centre and  
4 with 1:1 allocation between the intervention and control arm. Randomization will be  
5 performed centrally using the CommCare platform after eligibility criteria was confirmed,  
6 informed consent signed, and baseline information collected. Therefore, the randomized  
7 allocation will not be revealed until after a participant was formally entered into the trial.  
8 Therefore, concealment of allocation will be complete. The SMS will be automatically  
9 generated by the CommCare platform and unknown to the investigators in contact with  
10 patients.  
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15 Blinding: Because of the nature of the intervention (SMS messages), it is not possible to  
16 include blind participants. However, the tx2heart trial will perform a blinded assessment  
17 of outcomes. Research personnel collecting data on clinical events, adherence scales,  
18 and biomarkers will not have access to treatment allocation. The laboratory results will  
19 be performed once trial follow-up is completed.  
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### 25 **Data collection methods**

26  
27 Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered  
28 in the CommCare platform, designed by Dimagi. CommCare is an open source mobile  
29 platform designed for data collection, client management, decision support, and  
30 behaviour change communication. The electronic devices (desktop computers, laptops  
31 and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by  
32 Fundación Cardiovascular de Colombia.  
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38 Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while  
39 maximizing retention to follow-up. The following strategies to prevent loss to follow-up  
40 will be used. 1) One phone call at the third month of participation. Trained personnel  
41 different from the other interviewers will phone the participants to guarantee the blind  
42 design. Professionals in charge of the follow-up are trained in patient contact with the  
43 ability to empathize with volunteers. 2) We will register at least three relatives' numbers  
44 to contact in case we are not able to reach the patient, and we will phone the participant's  
45 relatives. 3) We will register the addresses of participants in case we cannot reach the  
46 patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the  
47 participants a contact phone number to let us to know if they change their phone number  
48 contact. We will explain these strategies to participants to get permission for further  
49 contact.  
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### 59 **Clinical outcomes**

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3 Death from cardiovascular causes and hospitalization due to nonfatal acute coronary  
4 syndrome, nonfatal stroke, or urgent revascularization will be defined by local  
5 investigators based on clinical notes and clear objective criteria using the suggestions  
6 provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular  
7 Endpoint Events in Clinical Trials<sup>18</sup>.  
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### 11 *Self-reported adherence*

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

40 Physiological measurements of heart rate and blood pressure will be measured using a  
41 calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by  
42 trained health care professionals. Patients will sit quietly for 10 minutes before the  
43 examinations.  
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47 Blood LDL-C: Quantification of serum LDL will be performed using automated equipment  
48 by a direct method.  
49

50 Recent large epidemiological studies confirmed that resting heart rate is an independent  
51 predictor of cardiovascular mortality. Heart rate decrease is itself an important  
52 mechanism of the benefit of the blockers and other drugs that reduce heart rate after an  
53 acute myocardial infarction<sup>(1-4)</sup>. Controversies on the optimal dose to obtain results  
54 remain, but the reduction in heart rate is notorious in patients receiving beta-blockers<sup>5</sup>.  
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58 In Colombia, beta-blockers are a first-line drug used for secondary prevention. The most  
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3 frequently beta-blocker is carvedilol, which exhibits advantages in decreasing heart rate  
4 and mortality in patients with some type of cardiovascular event<sup>6</sup>.  
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### 7 8 **Data management**

9 Data will be stored on a secure system and will be password protected. All trial  
10 procedures will be performed in accordance with the principles of Good Clinical Practice  
11 (GCP). Essential documents of the sponsor/trial organizers and investigators will be  
12 retained for at least 10 years after completion of the trial. The research staff will maintain  
13 appropriate medical and research records for this clinical study and meet with the  
14 regulatory and institutional frameworks for the protection of the confidentiality  
15 requirements. As sponsor of this trial, Fundación Cardiovascular de Colombia will allow  
16 regulatory agencies to examine (under applicable law) clinical records to check the  
17 quality, safety and progress of the study.  
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### 25 26 **Statistical Analysis**

27 The main analyses will be an “intention to treat”, meaning it will compare all patients  
28 allocated to the intervention to patients allocated to the control arm, regardless of  
29 whether they received the allocated intervention. A sensitivity per protocol analysis will  
30 also be performed. For continuous outcomes (including all primary outcomes: LDL  
31 cholesterol, blood pressure and Heart rate), we will estimate an ANCOVA model  
32 regressing the 12-month difference from baseline in the allocated group and the mean  
33 centred baseline values of the continuous variable. Deaths and hospitalizations will be  
34 analysed using Cox regression models to estimate hazard ratios. The assumptions  
35 underlying all of these models will be assessed. For subgroup analyses, we will only  
36 consider a limited number of variables that, given the mechanism of action of the  
37 intervention, could modify the effect of the intervention. A detailed statistical analysis plan  
38 setting out full details of the proposed analyses will be prepared and completed before  
39 the trial database is locked for final analysis. Missing data will be managed by an  
40 intention to treat analysis.  
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### 50 51 **Data Monitoring**

52 Data monitoring will be executed according to GCP Guidelines. This trial is a large,  
53 pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change  
54 behaviour and increase adherence of safe and proven effective interventions for  
55 secondary prevention that have been in clinical use for decades. Clinical management  
56 for underlying conditions will remain as per hospital’s standard protocol. Based on these  
57 factors, the probability of harm or injury (physical, psychological, social or economic)  
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3 occurring because of participation in this research study was assessed as low risk to  
4 participants in each of these categories. Based on the low risks associated with this trial,  
5 there will not be a data monitoring committee. However, a monitoring plan to ensure  
6 appropriate performance of the trial will be developed, which will incorporate 100%  
7 central monitoring in conjunction with procedures, such as investigator training and  
8 meetings and written guidance. All data will be subject to statistical monitoring, and at  
9 least 10% of data will be subjected to on-site monitoring. Investigators/institutions are  
10 required to provide direct access to source data/documents for trial-related monitoring,  
11 audits, ethics committee review and regulatory inspection. All trial-related and source  
12 documents must be kept for 15 years after the end of the trial.  
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### 20 **Patient and Public Involvement**

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

#### 34 **Protocol amendments**

35  
36 The protocol for the trial has not been modified.  
37  
38  
39

#### 40 **Ethical considerations**

41  
42 The study will be performed in compliance with the protocol, regulatory requirements,  
43 GCP and the ethical principles of the Declaration of Helsinki.  
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#### 47 **Ethical approval**

48  
49 The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and  
50 approved the trial.  
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52

#### 53 **Informed Consent:**

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55 The investigator or designated personnel will inform the patient of the objectives,  
56 methods, anticipated benefits and potential risks and inconveniences of the study. The  
57 patient will be given every opportunity to clarify any points he/she does not understand  
58 and, if necessary, ask for more information. Written consent must be given by the patient  
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3 and/or the legal guardian of the patient after detailed information about the study is  
4 provided in accordance with any national provisions on the protection of clinical study  
5 patients. The verbal explanation will cover all of the elements specified in the written  
6 information provided to the patient. Patients and/or legal guardians will be required to  
7 sign and date the informed consent form. Patients who refuse to give or who withdraw  
8 written informed consent will not be included or continue in the study. The trial will include  
9 a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or  
10 law of protection of personal data, where the study team is authorized to handle personal  
11 and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be  
12 recorded and stored for a set time. Eligible participants will only be included in the study  
13 after signing "Txt2Heart-Colombia" informed consent (testified, where required by law or  
14 regulation), as approved by the ethics committees. The process will be documented in  
15 the patient source documents, specifically in CRFs (Case Report Form).  
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25 Confidentiality: Information about the study subjects will be kept confidential. The  
26 investigators will ensure the anonymity of patients, and patients will not be identified by  
27 name in any document. Informed consent forms and patient recruitment registration will  
28 be kept strictly confidential only to permit identification of the patient at Fundación  
29 Cardiovascular de Colombia. Information about the study subjects will be handled under  
30 the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law  
31 of data protection). The regulations that require an authorization signed by the patient  
32 including the follow information: What protected health information (PHI) will be collected  
33 from the study subjects, who will have access to that information and why, who will use  
34 and disclose that information and the right to withdraw his/her authorization to use their  
35 PHI.  
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#### 45 **Access to data**

46 The principal investigator and sub-investigators will have access to the data to verify and  
47 analyse the results. To ensure confidentiality, all of the investigators will be blinded of  
48 participant identification.  
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#### 52 **Ancillary and post-trial care**

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

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## 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

1  
2  
3 intervention and studied the behavioural theories that support the intervention  
4 methodology.  
5

6  
7  
8 *Study chair*  
9

10  
11 Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University  
12 College London at Massachusetts Veterans Epidemiology Research and Information  
13 Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas  
14 conceived the idea of conducting the trial and participated in the methodology design of  
15 the trial.  
16  
17  
18

19  
20 Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology &  
21 Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived  
22 the idea of conducting the trial and participated in the methodology design of the trial.  
23  
24  
25

26  
27 *Sub-investigators:*  
28

29  
30 Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research  
31 Department of Primary Care and Population Health, University College London. Dr.  
32 Murray contributed in the intervention design and message validity process.  
33  
34  
35

36 David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population  
37 Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the  
38 statistical analysis and data management of the trial.  
39  
40  
41

42 Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London  
43 School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and  
44 participated in the validity process of the message intervention.  
45  
46  
47

48 Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins  
49 contributed in the message intervention design.  
50  
51  
52

53 Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of  
54 Pharmacy, University College London. Dr. Horne participated in the validity process of  
55 the message intervention and choosing adherence scales.  
56  
57  
58  
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1  
2  
3 Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación  
4 Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the  
5 processing design for biological samples.  
6  
7

8  
9 Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at  
10 Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.  
11  
12

13  
14 Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant  
15 researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez  
16 participated in the intervention design.  
17  
18

### 19 20 21 **Acknowledgments statement**

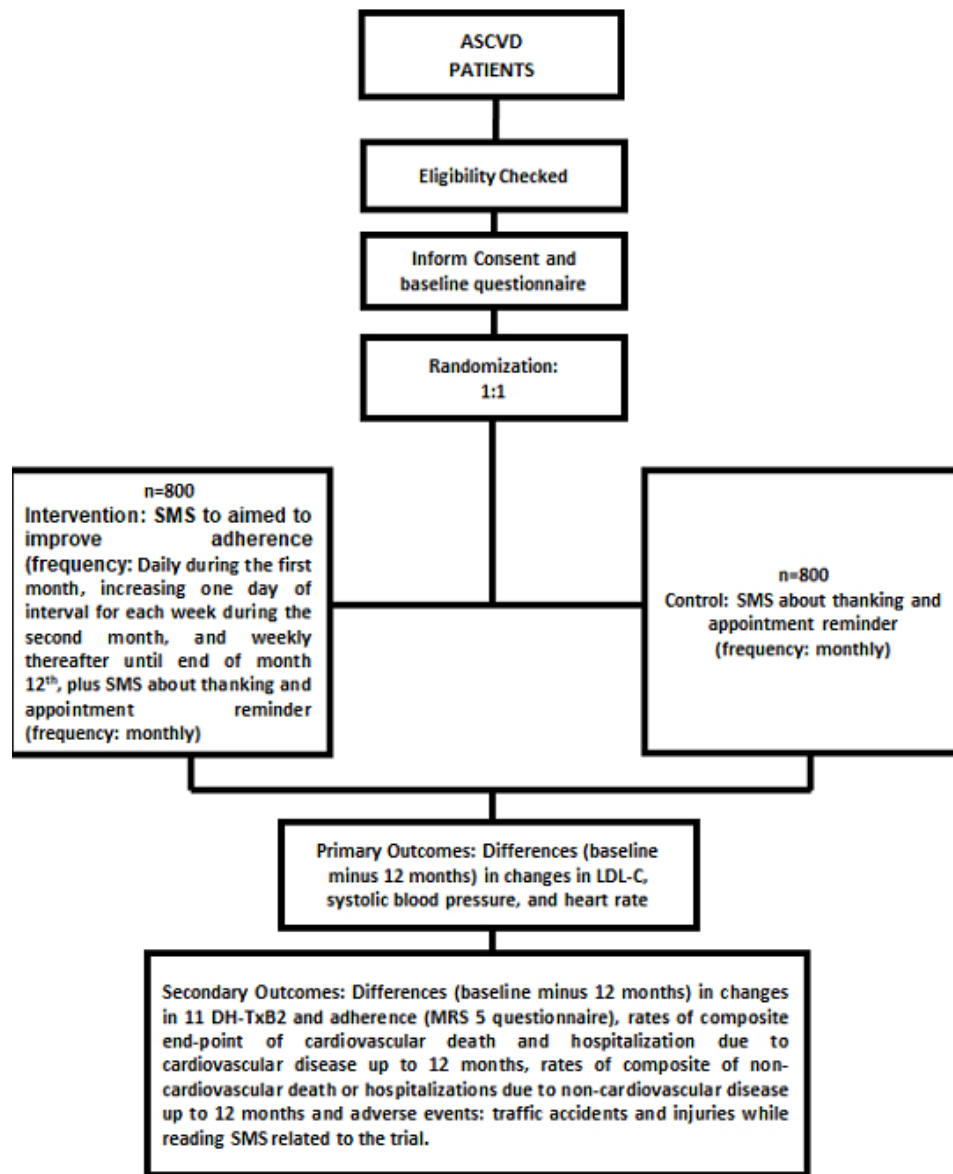
22  
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24 Colombia for their help with developing our research questions.  
25  
26

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29  
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36  
37 Universidad Pontificia Bolivariana, Bucaramanga sectional  
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### 40 41 **Competing interests' statement**

42  
43 All authors declare there is not conflict of interest.  
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45 All funding institutions declare there is not conflict of interest.  
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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: <a href="mailto:contacto@colciencias.gov.co">contacto@colciencias.gov.co</a> (+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	<p>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.</p> <p>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.</p>
Key inclusion and exclusion criteria	<p>Inclusion Criteria:</p> <p>Age <math>\geq 18</math> years old</p> <p>Sexes eligible for study: both</p> <p>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,</p> <p>peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).</p> <p>Own at least one mobile phone</p>

	<p>Ability to read and understand text messages (SMS)</p> <p>Intention to stay in the country of recruitment during the next 12 months</p> <p>Exclusion Criteria:</p> <p>Contraindication to take all cardiovascular medications used in secondary prevention.</p> <p>Participation in another randomized clinical trial that could interfere with adherence to treatment.</p>
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)	<p>Differences in changes (baseline minus 12 months) of:</p> <p>Low density lipoprotein cholesterol (LDL-C)</p> <p>Systolic Blood pressure</p> <p>Heart Rate</p>
Key secondary outcomes	<p>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.</p> <p>Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months.</p> <p>Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months</p> <p>Adverse events: traffic accidents and injuries while reading SMS related to the trial.</p>

# 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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	2
2				
3	data set		Registration Data Set	
4				
5				
6	Protocol version	<a href="#">#3</a>	Date and version identifier	15
7				
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9				
10	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
11				
12				
13	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	18
14				
15	responsibilities:			
16				
17	contributorship			
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20	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
21				
22	responsibilities:			
23				
24	sponsor contact			
25				
26	information			
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28				
29				
30	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	18
31				
32	responsibilities:		collection, management, analysis, and interpretation of	
33				
34	sponsor and funder		data; writing of the report; and the decision to submit the	
35				
36			report for publication, including whether they will have	
37				
38			ultimate authority over any of these activities	
39				
40				
41				
42	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	18
43				
44	responsibilities:		centre, steering committee, endpoint adjudication	
45				
46	committees		committee, data management team, and other individuals or	
47				
48			groups overseeing the trial, if applicable (see Item 21a for	
49				
50			data monitoring committee)	
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54	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
55				
56	rationale		undertaking the trial, including summary of relevant studies	
57				
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1		(published and unpublished) examining benefits and harms	
2			
3		for each intervention	
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6	Background and	<a href="#">#6b</a> Explanation for choice of comparators	7
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8	rationale: choice of		
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10	comparators		
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13	Objectives	<a href="#">#7</a> Specific objectives or hypotheses	7
14			
15			
16	Trial design	<a href="#">#8</a> Description of trial design including type of trial (eg, parallel	7
17		group, crossover, factorial, single group), allocation ratio,	
18		and framework (eg, superiority, equivalence, non-inferiority,	
19		exploratory)	
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26	Study setting	<a href="#">#9</a> Description of study settings (eg, community clinic,	8
27		academic hospital) and list of countries where data will be	
28		collected. Reference to where list of study sites can be	
29		obtained	
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43	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If applicable,	8
44		eligibility criteria for study centres and individuals who will	
45		perform the interventions (eg, surgeons, psychotherapists)	
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51	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	8
52		replication, including how and when they will be	
53	description	administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	9
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	10
12				
13	adherence		and any procedures for monitoring adherence (eg, drug	
14			tablet return; laboratory tests)	
15				
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18				
19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	8
20				
21	concomitant care		permitted or prohibited during the trial	
22				
23				
24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	13
25			specific measurement variable (eg, systolic blood pressure),	
26			analysis metric (eg, change from baseline, final value, time	
27			to event), method of aggregation (eg, median, proportion),	
28			and time point for each outcome. Explanation of the clinical	
29			relevance of chosen efficacy and harm outcomes is strongly	
30			recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	9
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly recommended	
44			(see Figure)	
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study	11
52			objectives and how it was determined, including clinical and	
53			statistical assumptions supporting any sample size	
54			calculations	
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	11
2			reach target sample size	
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6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	12
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a random	
9			sequence, details of any planned restriction (eg, blocking)	
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11			should be provided in a separate document that is	
12			unavailable to those who enrol participants or assign	
13			interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	12
24	concealment		central telephone; sequentially numbered, opaque, sealed	
25			envelopes), describing any steps to conceal the sequence	
26	mechanism		until interventions are assigned	
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	12
34	implementation		participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12
42			trial participants, care providers, outcome assessors, data	
43			analysts), and how	
44				
45				
46				
47				
48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
51	unblinding			
52				
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56	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	13
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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

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15	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-
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17	retention		up, including list of any outcome data to be collected for
18			participants who discontinue or deviate from intervention
19			protocols
20			
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25	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including
26			
27			any related processes to promote data quality (eg, double
28			data entry; range checks for data values). Reference to
29			where details of data management procedures can be
30			found, if not in the protocol
31			
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37	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
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39			outcomes. Reference to where other details of the statistical
40			analysis plan can be found, if not in the protocol
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44	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and
45			
46	analyses		adjusted analyses)
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50	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-
51			
52	population and		adherence (eg, as randomised analysis), and any statistical
53			
54	missing data		methods to handle missing data (eg, multiple imputation)
55			
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57	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary
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1	formal committee		of its role and reporting structure; statement of whether it is	
2			independent from the sponsor and competing interests; and	
3			reference to where further details about its charter can be	
4			found, if not in the protocol. Alternatively, an explanation of	
5			why a DMC is not needed	
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12	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	15
13	interim analysis		including who will have access to these interim results and	
14			make the final decision to terminate the trial	
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20	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	17
21			solicited and spontaneously reported adverse events and	
22			other unintended effects of trial interventions or trial conduct	
23				
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28	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any,	15
29			and whether the process will be independent from	
30			investigators and the sponsor	
31				
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35	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional	15
36	approval		review board (REC / IRB) approval	
37				
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41	Protocol	<a href="#">#25</a>	Plans for communicating important protocol modifications	15
42	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
43			relevant parties (eg, investigators, REC / IRBs, trial	
44			participants, trial registries, journals, regulators)	
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51	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential	16
52			trial participants or authorised surrogates, and how (see	
53			Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	16
2				
3	ancillary studies		participant data and biological specimens in ancillary	
4			studies, if applicable	
5				
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7				
8	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	16
9			participants will be collected, shared, and maintained in	
10			order to protect confidentiality before, during, and after the	
11			trial	
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18	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	16
19	interests		investigators for the overall trial and each study site	
20				
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24	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	16
25			and disclosure of contractual agreements that limit such	
26			access for investigators	
27				
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30				
31	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	16
32	trial care		compensation to those who suffer harm from trial	
33			participation	
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39	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	17
40	trial results		results to participants, healthcare professionals, the public,	
41			and other relevant groups (eg, via publication, reporting in	
42			results databases, or other data sharing arrangements),	
43			including any publication restrictions	
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51	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	17
52	authorship		professional writers	
53				
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57	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	17
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1	reproducible	participant-level dataset, and statistical code	
2			
3	research		
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6	Informed consent	<a href="#">#32</a> Model consent form and other related documentation given	16
7			
8	materials	to participants and authorised surrogates	
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11	Biological specimens	<a href="#">#33</a> Plans for collection, laboratory evaluation, and storage of	13
12			
13		biological specimens for genetic or molecular analysis in the	
14			
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16		current trial and for future use in ancillary studies, if	
17			
18		applicable	
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22 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
23 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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

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3 **Evaluation of the efficacy and safety of text messages targeting adherence to**  
4 **cardiovascular medications in secondary prevention: The Txt2heart-Colombia**  
5 **randomized controlled trial protocol**  
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27 mHealth, text messaging  
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30  
31 **Word count:** 5006  
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### 34 Abstract

35  
36 **Introduction:** Anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are  
37 cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for  
38 reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that  
39 adherence to these cardiovascular medications is far from ideal. A recent Cochrane  
40 review showed a potential beneficial effect of SMS interventions on adherence to  
41 medication in ASCVD patients.  
42

43 **Methods and analysis:** The Txt2heart study is a pragmatic randomized single-blind  
44 controlled trial. The objective is to evaluate the efficacy and safety of an intervention with  
45 SMS messages delivered by mobile phones to improve adherence to cardiovascular  
46 medications in patients with ASCVD. The intervention consists of behavioural techniques  
47 delivered via SMS. The primary outcome is change in blood serum low-density  
48 lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins. Secondary  
49 outcomes will include systolic blood pressure as an indicator of adherence to blood-  
50 lowering therapies and heart rate as an indicator of adherence to beta-blockers, urine  
51 levels of 11-dehydrothromboxane B<sub>2</sub> (11dhTxB<sub>2</sub>), self-reported adherence to  
52 cardiovascular medications and rates of cardiovascular death or hospitalization due to  
53 cardiovascular disease.  
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55

56 **Ethics and dissemination:** The study will be performed in compliance with the protocol,  
57 regulatory requirements, Good Clinical Practice and ethical principles of the Declaration  
58 of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated  
59 and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to  
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3 evaluate whether SMS messages delivered through mobile telephones change the  
4 behaviour of Colombian patients who have suffered a cardiovascular event. Trial results  
5 will be presented to the local health authorities, and if the intervention is effective and  
6 safe, we hope this strategy will be implemented quickly because of its low cost and wide-  
7 reaching impact on the population.  
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11 **Trial registration number:** ClinicalTrials.gov: NCT03098186  
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### 14 15 **Strengths and limitations of this study.** 16

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19 The trial uses an innovative intervention through SMS methodology based on behaviour  
20 theories.  
21

22 The trial uses biomarkers to evaluate medication adherence.  
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24 The trial is the largest evaluating SMS to increase adherence for cardiovascular  
25 secondary prevention  
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27 Measuring adherence is challenging; we are triangulating data from biomarkers and self-  
28 reported adherence to improve the accuracy of the trial measure of effect  
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### 31 **INTRODUCTION** 32

33 Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death  
34 worldwide. Approximately 35 million people worldwide have an acute coronary event or  
35 cerebrovascular event annually, and one quarter of these events occur in people with  
36 established ASCVD<sup>1</sup>. These arterial occlusive events occur at an early age in low and  
37 middle-income countries (LMICs), which affects economically active populations and  
38 results in large economic impacts<sup>2</sup>.  
39

40 Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet  
41 therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the  
42 risk of ASCVD events in patients with established ASCVD, and these agents are included  
43 in the list of the World Health Organization (WHO) Essential Medicines List (EML)<sup>3</sup>.  
44 Treatment with these four proven medications (together with smoking cessation)  
45 prevents or postpones approximately 75-80% of recurrent vascular events and their  
46 complications, such as death and disability<sup>4</sup>.  
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49 Unfortunately, there is abundant evidence that the worldwide adherence to these  
50 cardiovascular medications in patients with ASCVD is far from ideal. Less than half of  
51 patients with known ASCVD disease in high-income countries are receiving this group  
52 of cardiovascular medications, and the situation is much worse in LMICs. The PURE  
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3 study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types  
4 of cardiovascular drugs<sup>5</sup>.

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

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

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

51 A recent Cochrane review evaluated the effects of SMS on adherence to medications in  
52 patients with ASCVD<sup>12</sup>. The review identified seven trials (1310 participants) and showed  
53 a beneficial effect of SMS on adherence to medications in six of these trials. However,  
54 the quality of the evidence was very low. The Cochrane review identified the following  
55 limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a  
56 short follow-up (<6 months); (III) primary outcomes reported were of limited clinical  
57 relevance; (IV) most studies recruited only patients with acute coronary syndrome, which  
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3 leaves out an important group of patients with other arterial occlusive events (e.g.,  
4 ischaemic stroke, peripheral vascular disease and programmed coronary  
5 revascularizations) who should be amenable for this type of intervention; (V) few studies  
6 were performed in LMICs; and (VI) most trials did not describe the processes behind the  
7 SMS content generation, and the few trials that did report these processes did not target  
8 the key knowledge and attitudinal factors that are known to influence adherence to  
9 medication; instead the interventions were simple “reminders”.

10  
11 In conclusion, given the high prevalence of people with ASCVD in LMICs and the low  
12 use of cost-effective secondary prevention medications, a low-cost intervention that  
13 builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to  
14 improve public health. The current evidence shows that SMS interventions based on  
15 behaviour-change techniques are a potentially effective strategy to increase adherence  
16 to medications in people with ASCVD. However, further large trials are needed.

17  
18 To provide the high-quality evidence needed to assess the effect of SMS interventions  
19 based on behaviour-change techniques to increase adherence to medications in patients  
20 with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority  
21 parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the  
22 efficacy and safety of SMS on adherence to cardiovascular medications. The trial is  
23 being performed in a setting (Colombia) where patient factors, such as knowledge,  
24 attitudes and beliefs, are important determinants of adherence. In this context, medicines  
25 are widely available and generally affordable, so an intervention delivered to patients via  
26 SMS has the potential to be effective.

## 37 38 39 **METHODS AND ANALYSIS**

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42 This protocol is reported following the SPIRIT Standard Protocol Items recommendations  
43 for Interventional Trials<sup>13</sup> (see supplementary file 1).

### 44 45 46 **Aim and objectives**

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48 The primary objective is to evaluate the efficacy and safety of an intervention with  
49 SMS messages delivered by mobiles phones to improve adherence to  
50 cardiovascular medications in patients with atherosclerotic cardiovascular disease  
51 (ASCVD). We will assess the intervention efficacy via the measurement of blood  
52 serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as  
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3 an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart  
4 rate as an indicator of adherence to beta-blockers.  
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8 The secondary objective is to assess the impact of mobile text messaging on self-  
9 reported adherence to medications, hospitalizations, and the composite end-point of  
10 incident Major Adverse Cardiovascular Events (MACE) at 12 months.  
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### 13 14 **Choice of comparator**

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

34 Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled  
35 trial. This design is aimed to minimize any potential bias that affects the internal validity  
36 of the study. The selection criteria were designed to increase the number of potential  
37 beneficiaries of the intervention and to keep the selection process as close as possible  
38 to the future scenario in which the intervention will be implemented. Therefore,  
39 Txt2Heart-Colombia is pragmatic in design. The active intervention will be the SMS  
40 delivered to mobile phones, and the content of the SMS is aimed to modify behaviours  
41 associated with poor adherence to ASCVD medications in ASCVD patients.  
42 Randomization will be performed as block randomization with a 1:1 allocation.  
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### 50 **Study setting**

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

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3 Inclusion criteria: Adult patients  $\geq 18$  years old with a history of at least one of the following  
4 arterial occlusive events will be included: acute coronary syndrome (unstable angina,  
5 acute myocardial infarction with or without ST elevation), stable angina, ischaemic  
6 cerebrovascular disease, peripheral arterial disease or coronary revascularization  
7 (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary  
8 angioplasty (PTCA). Patients should own a mobile phone and be able to read SMS.  
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12 Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular  
13 secondary prevention medications.  
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### 16 17 **Intervention**

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19 The intervention under evaluation consists of *behavioural change techniques* (BCTs)  
20 delivered via SMS. We developed our intervention following the recommendations of  
21 Abroms et al<sup>14</sup>. First, we reviewed the literature on individual level factors that influence  
22 adherence to medication. We performed country-specific qualitative studies using focus  
23 group discussions and semi-structured interviews to evaluate cardiovascular patients'  
24 perceptions about mHealth programmes to determine the necessary content and  
25 preferred timing and frequency of the SMS messages. To construct the content of the  
26 SMS, we wrote messages using educational and enabling behaviour change functions  
27 and established BCTs to target the potentially modifiable factors that influence the  
28 adherence referred to in the literature and found in our qualitative studies<sup>15</sup>. Finally, we  
29 tested the SMS messages with participants and adapted the messages based on their  
30 feedback to ensure the messages were understandable, acceptable, and relevant<sup>16</sup>. The  
31 resultant intervention delivered by SMS provides information about health consequences  
32 of adherence or non-adherence, instruction on how to take medication, medicine-taking  
33 prompts and cues, support in establishing medicine-taking habits, reframing medicine-  
34 taking and provides or encourages social support for taking medication<sup>17</sup>. The messages  
35 were designed according to the Transtheoretical Model (TTM) (Prochaska &  
36 DiClemente, 1992) and were aimed to enhance actions related to the steps and  
37 processes of this model. We will send messages daily the first month, three times per  
38 week the second month and once weekly the last ten months. This reducing frequency  
39 is consistent with the TTM, which suggests that people in the early stages of change  
40 require more intense input than people in later stages. In accordance with data from the  
41 focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The  
42 intervention will be delivered through an electronic platform, and it will be a one-way  
43 intervention. We will explain patients that they should not answer the messages, but they  
44 will be able to request to stop receiving the messages and withdraw from the trial by  
45 sending a message with the word "STOP". We will explain to patients that they should  
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3 send the 'stop' message in this situation. Stop messages will be saved and monitored  
4 by a trained engineer, separate from the study team, in order to maintain blinding.  
5 Similarly, a trained engineer, separate from the study team, will save and monitor the  
6 patients' answers if they respond to the messages. Because of the pragmatic nature of  
7 our study we will not tailor the messages. The trial intervention will start the day after  
8 recruitment and continue for 12 months or until the participant withdraws from the study  
9 or dies. The follow-up duration will be at least 12 months to a maximum of 36 months.  
10 Participants will not receive messages after month 12.  
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### 17 **Outcomes**

18 The primary outcome was selected for its clinical relevance and include: differences in  
19 changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of  
20 adherence to statins.  
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24 The following secondary outcomes will be included: *systolic blood pressure* as an  
25 indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs), *heart rate*  
26 as an indicator of adherence to beta-blockers, *urine levels of 11 dhTxB2* as an indicator  
27 of adherence to antiplatelet therapy; *self-reported adherence to cardiovascular*  
28 *medications* used in secondary prevention as measured using the MARS-5  
29 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular  
30 disease and non-cardiovascular death or hospitalizations due to non-cardiovascular  
31 disease. We will also include road traffic crashes (the only potential known hazard of text  
32 messaging) and death due to all causes as secondary outcomes.  
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### 41 **Participant timeline**

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

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3 Randomization: We will use block randomization (varying size), stratifying by centre and  
4 with 1:1 allocation between the intervention and control arm. Randomization will be  
5 performed centrally using the CommCare platform after eligibility criteria was confirmed,  
6 informed consent signed, and baseline information collected. Therefore, the randomized  
7 allocation will not be revealed until after a participant was formally entered into the trial.  
8 Therefore, concealment of allocation will be complete. The SMS will be automatically  
9 generated by the CommCare platform and unknown to the investigators in contact with  
10 patients.  
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15 Blinding: Because of the nature of the intervention (SMS messages), it is not possible to  
16 include blind participants. However, the tx2heart trial will perform a blinded assessment  
17 of outcomes. Research personnel collecting data on clinical events, adherence scales,  
18 and biomarkers will not have access to treatment allocation. The laboratory results will  
19 be performed once trial follow-up is completed.  
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### 24 25 **Data collection methods**

26  
27 Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered  
28 in the CommCare platform, designed by Dimagi. CommCare is an open source mobile  
29 platform designed for data collection, client management, decision support, and  
30 behaviour change communication. The electronic devices (desktop computers, laptops  
31 and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by  
32 Fundación Cardiovascular de Colombia.  
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38 Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while  
39 maximizing retention to follow-up. The following strategies to prevent loss to follow-up  
40 will be used. 1) One phone call at the third month of participation. Trained personnel  
41 different from the other interviewers will phone the participants to guarantee the blind  
42 design. Professionals in charge of the follow-up are trained in patient contact with the  
43 ability to empathize with volunteers. 2) We will register at least three relatives' numbers  
44 to contact in case we are not able to reach the patient, and we will phone the participant's  
45 relatives. 3) We will register the addresses of participants in case we cannot reach the  
46 patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the  
47 participants a contact phone number to let us to know if they change their phone number  
48 contact. We will explain these strategies to participants to get permission for further  
49 contact.  
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### 59 **Clinical outcomes**

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3 Death from cardiovascular causes and hospitalization due to nonfatal acute coronary  
4 syndrome, nonfatal stroke, or urgent revascularization will be defined by local  
5 investigators based on clinical notes and clear objective criteria using the suggestions  
6 provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular  
7 Endpoint Events in Clinical Trials<sup>18</sup>.  
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### 11 *Self-reported adherence*

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

25 In order to complete information about medications, we will ask patients about prescribed  
26 medication.  
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### 35 *Biomarkers*

36 Physiological measurements of heart rate and blood pressure will be measured using a  
37 calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by  
38 trained health care professionals. Patients will sit quietly for 10 minutes before the  
39 examinations.  
40

41 Blood LDL-C: Quantification of serum LDL will be performed using automated equipment  
42 by a direct method.  
43

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

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

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

50 Data monitoring will be executed according to GCP Guidelines. This trial is a large,  
51 pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change  
52 behaviour and increase adherence of safe and proven effective interventions for  
53 secondary prevention that have been in clinical use for decades. Clinical management  
54 for underlying conditions will remain as per hospital's standard protocol. Based on these  
55 factors, the probability of harm or injury (physical, psychological, social or economic)  
56 occurring because of participation in this research study was assessed as low risk to  
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3 participants in each of these categories. Based on the low risks associated with this trial,  
4 there will not be a data monitoring committee. However, a monitoring plan to ensure  
5 appropriate performance of the trial will be developed, which will incorporate 100%  
6 central monitoring in conjunction with procedures, such as investigator training and  
7 meetings and written guidance. All data will be subject to statistical monitoring, and at  
8 least 10% of data will be subjected to on-site monitoring. Investigators/institutions are  
9 required to provide direct access to source data/documents for trial-related monitoring,  
10 audits, ethics committee review and regulatory inspection. All trial-related and source  
11 documents must be kept for 15 years after the end of the trial.  
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### 19 **Patient and Public Involvement**

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

### 33 **Protocol amendments**

34 The protocol for the trial has not been modified.  
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36  
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38

### 39 **Ethical considerations**

40 The study will be performed in compliance with the protocol, regulatory requirements,  
41 GCP and the ethical principles of the Declaration of Helsinki.  
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### 45 **Ethical approval**

46 The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and  
47 approved the trial.  
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### 51 **Informed Consent:**

52 The investigator or designated personnel will inform the patient of the objectives,  
53 methods, anticipated benefits and potential risks and inconveniences of the study. The  
54 patient will be given every opportunity to clarify any points he/she does not understand  
55 and, if necessary, ask for more information. Written consent must be given by the patient  
56 and/or the legal guardian of the patient after detailed information about the study is  
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3 provided in accordance with any national provisions on the protection of clinical study  
4 patients. The verbal explanation will cover all of the elements specified in the written  
5 information provided to the patient. Patients and/or legal guardians will be required to  
6 sign and date the informed consent form. Patients who refuse to give or who withdraw  
7 written informed consent will not be included or continue in the study. The trial will include  
8 a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or  
9 law of protection of personal data, where the study team is authorized to handle personal  
10 and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be  
11 recorded and stored for a set time. Eligible participants will only be included in the study  
12 after signing "Txt2Heart-Colombia" informed consent (testified, where required by law or  
13 regulation), as approved by the ethics committees. The process will be documented in  
14 the patient source documents, specifically in CRFs (Case Report Form).  
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24 Confidentiality: Information about the study subjects will be kept confidential. The  
25 investigators will ensure the anonymity of patients, and patients will not be identified by  
26 name in any document. Informed consent forms and patient recruitment registration will  
27 be kept strictly confidential only to permit identification of the patient at Fundación  
28 Cardiovascular de Colombia. Information about the study subjects will be handled under  
29 the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law  
30 of data protection). The regulations that require an authorization signed by the patient  
31 including the follow information: What protected health information (PHI) will be collected  
32 from the study subjects, who will have access to that information and why, who will use  
33 and disclose that information and the right to withdraw his/her authorization to use their  
34 PHI.  
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#### 43 **Access to data**

44 The principal investigator and sub-investigators will have access to the data to verify and  
45 analyse the results. To ensure confidentiality, all of the investigators will be blinded of  
46 participant identification.  
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#### 50 **Ancillary and post-trial care**

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

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## 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

1  
2  
3 Anderson Bermon, MD, MSc: associate researcher and epidemiologist at Fundación  
4 Cardiovascular de Colombia, Demography and Biostatistics PhD student at CES  
5 University. Dr. Bermon participated in the trial design and studied the impact of the  
6 results in Colombia, considering the healthcare system limitations.  
7  
8

9  
10  
11 Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor  
12 Faculty of Psychology, Pontificia Bolivariana University. Dr. Uribe designed the message  
13 intervention and studied the behavioural theories that support the intervention  
14 methodology.  
15  
16

### 17 18 19 *Study chair*

20  
21  
22 Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University  
23 College London at Massachusetts Veterans Epidemiology Research and Information  
24 Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas  
25 conceived the idea of conducting the trial and participated in the methodology design of  
26 the trial.  
27  
28

29  
30  
31 Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology &  
32 Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived  
33 the idea of conducting the trial and participated in the methodology design of the trial.  
34  
35

### 36 37 38 *Sub-investigators:*

39  
40  
41 Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research  
42 Department of Primary Care and Population Health, University College London. Dr.  
43 Murray contributed in the intervention design and message validity process.  
44  
45

46  
47 David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population  
48 Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the  
49 statistical analysis and data management of the trial.  
50  
51

52  
53 Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London  
54 School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and  
55 participated in the validity process of the message intervention.  
56  
57  
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1  
2  
3 Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins  
4 contributed in the message intervention design.  
5  
6

7  
8 Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of  
9 Pharmacy, University College London. Dr. Horne participated in the validity process of  
10 the message intervention and choosing adherence scales.  
11  
12

13  
14 Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación  
15 Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the  
16 processing design for biological samples.  
17  
18

19  
20 Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at  
21 Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.  
22  
23

24  
25 Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant  
26 researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez  
27 participated in the intervention design.  
28  
29

### 30 31 32 **Acknowledgments statement**

33 We thank the Cardiology Department medical staff at Fundación Cardiovascular de  
34 Colombia for their help with developing our research questions.  
35  
36

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41 Fundación Cardiovascular de Colombia, Floridablanca

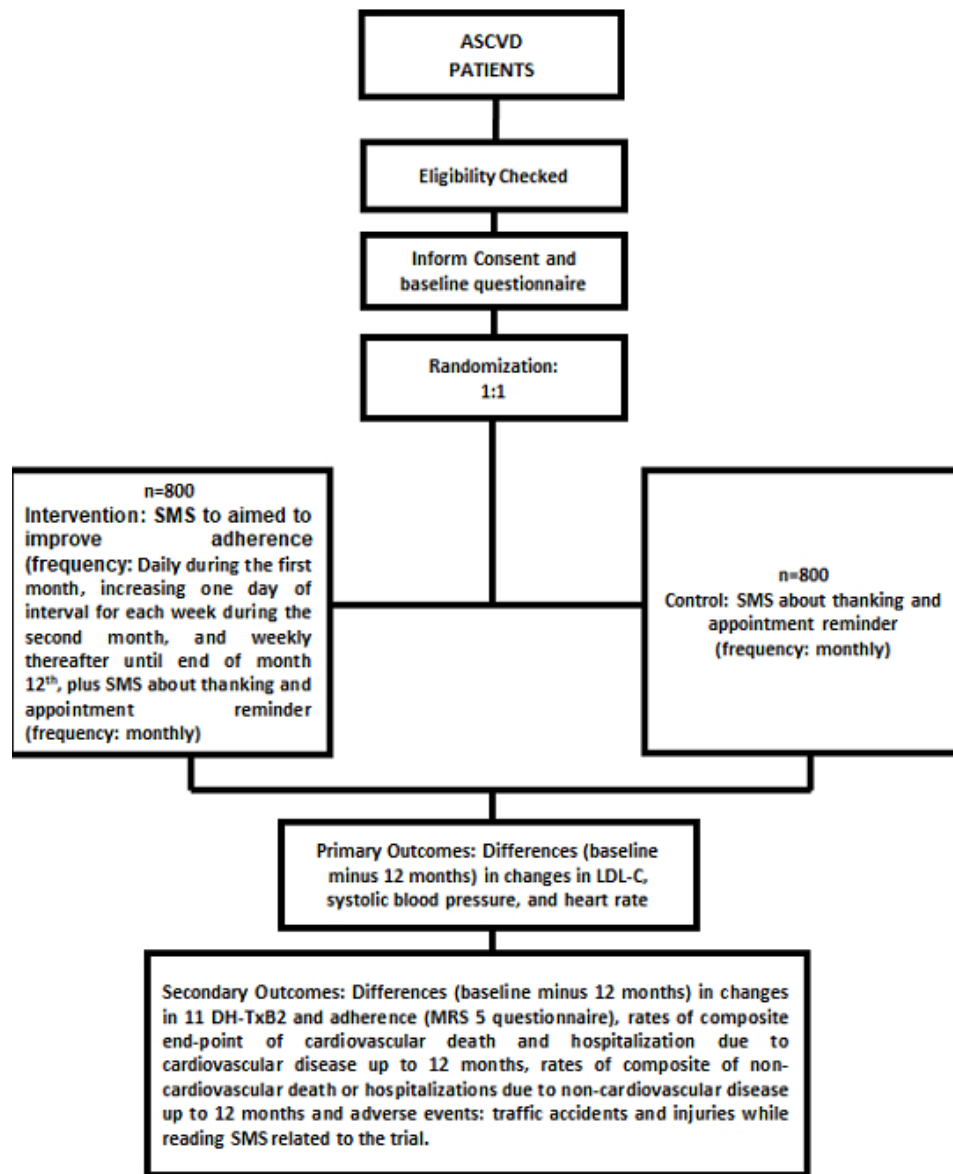
42 London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded  
43 Reference MR/N021304/1

44 Universidad Pontificia Bolivariana, Bucaramanga sectional  
45  
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47

### 48 49 50 51 **Competing interests' statement**

52 All authors declare there is not conflict of interest.

53 All funding institutions declare there is not conflict of interest.  
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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: <a href="mailto:contacto@colciencias.gov.co">contacto@colciencias.gov.co</a> (+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	<p>Acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation)</p> <p>Stable angina</p> <p>Ischemic cerebrovascular disease</p> <p>Peripheral arterial disease</p>
Interventions	<p>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.</p> <p>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.</p>
Key inclusion and exclusion criteria	<p>Inclusion Criteria:</p> <p>Age <math>\geq 18</math> years old</p> <p>Sexes eligible for study: both</p> <p>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,</p> <p>peripheral arterial disease or coronary revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA).</p> <p>Own at least one mobile phone</p>

	<p>Ability to read and understand text messages (SMS)</p> <p>Intention to stay in the country of recruitment during the next 12 months</p> <p>Exclusion Criteria:</p> <p>Contraindication to take all cardiovascular medications used in secondary prevention.</p> <p>Participation in another randomized clinical trial that could interfere with adherence to treatment.</p>
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)	<p>Differences in changes (baseline minus 12 months) of:</p> <p>Low density lipoprotein cholesterol (LDL-C)</p> <p>Systolic Blood pressure</p> <p>Heart Rate</p>
Key secondary outcomes	<p>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.</p> <p>Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months.</p> <p>Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months</p> <p>Adverse events: traffic accidents and injuries while reading SMS related to the trial.</p>

# 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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1



1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	2
2				
3	data set		Registration Data Set	
4				
5				
6	Protocol version	<a href="#">#3</a>	Date and version identifier	15
7				
8				
9				
10	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
11				
12				
13	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	18
14				
15	responsibilities:			
16				
17	contributorship			
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20	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
21				
22	responsibilities:			
23				
24	sponsor contact			
25				
26	information			
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28				
29				
30	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	18
31				
32	responsibilities:		collection, management, analysis, and interpretation of	
33				
34	sponsor and funder		data; writing of the report; and the decision to submit the	
35				
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42	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	18
43				
44	responsibilities:		centre, steering committee, endpoint adjudication	
45				
46	committees		committee, data management team, and other individuals or	
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54	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
55				
56	rationale		undertaking the trial, including summary of relevant studies	
57				
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1		(published and unpublished) examining benefits and harms	
2			
3		for each intervention	
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5			
6	Background and	<a href="#">#6b</a> Explanation for choice of comparators	7
7			
8	rationale: choice of		
9			
10	comparators		
11			
12			
13	Objectives	<a href="#">#7</a> Specific objectives or hypotheses	7
14			
15			
16	Trial design	<a href="#">#8</a> Description of trial design including type of trial (eg, parallel	7
17		group, crossover, factorial, single group), allocation ratio,	
18		and framework (eg, superiority, equivalence, non-inferiority,	
19		exploratory)	
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26	Study setting	<a href="#">#9</a> Description of study settings (eg, community clinic,	8
27		academic hospital) and list of countries where data will be	
28		collected. Reference to where list of study sites can be	
29		obtained	
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43	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If applicable,	8
44		eligibility criteria for study centres and individuals who will	
45		perform the interventions (eg, surgeons, psychotherapists)	
46			
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51	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	8
52		replication, including how and when they will be	
53	description	administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	9
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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7				
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10				
11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	10
12				
13	adherence		and any procedures for monitoring adherence (eg, drug	
14			tablet return; laboratory tests)	
15				
16				
17				
18				
19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	8
20				
21	concomitant care		permitted or prohibited during the trial	
22				
23				
24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	13
25			specific measurement variable (eg, systolic blood pressure),	
26			analysis metric (eg, change from baseline, final value, time	
27			to event), method of aggregation (eg, median, proportion),	
28			and time point for each outcome. Explanation of the clinical	
29			relevance of chosen efficacy and harm outcomes is strongly	
30			recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	9
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly recommended	
44			(see Figure)	
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study	11
52			objectives and how it was determined, including clinical and	
53			statistical assumptions supporting any sample size	
54			calculations	
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	11
2			reach target sample size	
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6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	12
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a random	
9			sequence, details of any planned restriction (eg, blocking)	
10				
11			should be provided in a separate document that is	
12			unavailable to those who enrol participants or assign	
13			interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	12
24	concealment		central telephone; sequentially numbered, opaque, sealed	
25			envelopes), describing any steps to conceal the sequence	
26	mechanism		until interventions are assigned	
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	12
34	implementation		participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12
42			trial participants, care providers, outcome assessors, data	
43			analysts), and how	
44				
45				
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47				
48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
51	unblinding			
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56	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	13
57				
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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

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15	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-
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17	retention		up, including list of any outcome data to be collected for
18			participants who discontinue or deviate from intervention
19			protocols
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25	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including
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27			any related processes to promote data quality (eg, double
28			data entry; range checks for data values). Reference to
29			where details of data management procedures can be
30			found, if not in the protocol
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37	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
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39			outcomes. Reference to where other details of the statistical
40			analysis plan can be found, if not in the protocol
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44	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and
45			
46	analyses		adjusted analyses)
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50	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-
51			
52	population and		adherence (eg, as randomised analysis), and any statistical
53			
54	missing data		methods to handle missing data (eg, multiple imputation)
55			
56			
57	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary
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1	formal committee		of its role and reporting structure; statement of whether it is	
2			independent from the sponsor and competing interests; and	
3			reference to where further details about its charter can be	
4			found, if not in the protocol. Alternatively, an explanation of	
5			why a DMC is not needed	
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12	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	15
13	interim analysis		including who will have access to these interim results and	
14			make the final decision to terminate the trial	
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20	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	17
21			solicited and spontaneously reported adverse events and	
22			other unintended effects of trial interventions or trial conduct	
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28	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any,	15
29			and whether the process will be independent from	
30			investigators and the sponsor	
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35	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional	15
36	approval		review board (REC / IRB) approval	
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41	Protocol	<a href="#">#25</a>	Plans for communicating important protocol modifications	15
42	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
43			relevant parties (eg, investigators, REC / IRBs, trial	
44			participants, trial registries, journals, regulators)	
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51	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential	16
52			trial participants or authorised surrogates, and how (see	
53			Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	16
2				
3	ancillary studies		participant data and biological specimens in ancillary	
4			studies, if applicable	
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8	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	16
9			participants will be collected, shared, and maintained in	
10			order to protect confidentiality before, during, and after the	
11			trial	
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18	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	16
19	interests		investigators for the overall trial and each study site	
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24	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	16
25			and disclosure of contractual agreements that limit such	
26			access for investigators	
27				
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30				
31	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	16
32	trial care		compensation to those who suffer harm from trial	
33			participation	
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39	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	17
40	trial results		results to participants, healthcare professionals, the public,	
41			and other relevant groups (eg, via publication, reporting in	
42			results databases, or other data sharing arrangements),	
43			including any publication restrictions	
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51	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	17
52	authorship		professional writers	
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57	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	17
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1	reproducible	participant-level dataset, and statistical code	
2			
3	research		
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6	Informed consent	<a href="#">#32</a> Model consent form and other related documentation given	16
7			
8	materials	to participants and authorised surrogates	
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11	Biological specimens	<a href="#">#33</a> Plans for collection, laboratory evaluation, and storage of	13
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13		biological specimens for genetic or molecular analysis in the	
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16		current trial and for future use in ancillary studies, if	
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18		applicable	
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22 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
23 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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

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Secondary Subject Heading:	Cardiovascular medicine, Health informatics, Health services research
Keywords:	Cardiovascular diseases, Health behavior, Medications adherence, mHealth, SMS, text messaging

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

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26 **Keywords:** Cardiovascular diseases, Health behavior, Medications adherence,  
27 mHealth, text messaging  
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31 **Word count:** 5006  
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### 34 **Abstract**

35  
36 **Introduction:** Anti-platelet therapy, ACE inhibitors/ARB, beta-blockers and statins are  
37 cost-effective in patients with atherosclerotic cardiovascular diseases (ASCVD) for  
38 reducing the risk of ASCVD events. Unfortunately, there is abundant evidence that  
39 adherence to these cardiovascular medications is far from ideal. A recent Cochrane  
40 review showed a potential beneficial effect of SMS interventions on adherence to  
41 medication in ASCVD patients.  
42

43 **Methods and analysis:** The Txt2heart study is a pragmatic randomized single-blind  
44 controlled trial. The objective is to evaluate the efficacy and safety of an intervention with  
45 SMS messages delivered by mobile phones to improve adherence to cardiovascular  
46 medications in patients with ASCVD. The intervention consists of behavioural techniques  
47 delivered via SMS. The primary outcome is change in blood serum low-density  
48 lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins. Secondary  
49 outcomes will include systolic blood pressure as an indicator of adherence to blood-  
50 lowering therapies and heart rate as an indicator of adherence to beta-blockers, urine  
51 levels of 11-dehydrothromboxane B<sub>2</sub> (11dhTxB<sub>2</sub>), self-reported adherence to  
52 cardiovascular medications and rates of cardiovascular death or hospitalization due to  
53 cardiovascular disease.  
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55

56 **Ethics and dissemination:** The study will be performed in compliance with the protocol,  
57 regulatory requirements, Good Clinical Practice and ethical principles of the Declaration  
58 of Helsinki. The Ethics Committee of Fundación Cardiovascular de Colombia evaluated  
59 and approved the trial. The Txt2heart Colombia trial aims to provide robust evidence to  
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3 evaluate whether SMS messages delivered through mobile telephones change the  
4 behaviour of Colombian patients who have suffered a cardiovascular event. Trial results  
5 will be presented to the local health authorities, and if the intervention is effective and  
6 safe, we hope this strategy will be implemented quickly because of its low cost and wide-  
7 reaching impact on the population.  
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11 **Trial registration number:** ClinicalTrials.gov: NCT03098186  
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### 14 15 **Strengths and limitations of this study.** 16

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19 The trial uses an innovative intervention through SMS methodology based on behaviour  
20 theories.  
21

22 The trial uses biomarkers to evaluate medication adherence.  
23

24 The trial is the largest evaluating SMS to increase adherence for cardiovascular  
25 secondary prevention  
26

27 Measuring adherence is challenging; we are triangulating data from biomarkers and self-  
28 reported adherence to improve the accuracy of the trial measure of effect  
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### 31 **INTRODUCTION** 32

33 Atherosclerotic cardiovascular diseases (ASCVD) are the main cause of death  
34 worldwide. Approximately 35 million people worldwide have an acute coronary event or  
35 cerebrovascular event annually, and one quarter of these events occur in people with  
36 established ASCVD<sup>1</sup>. These arterial occlusive events occur at an early age in low and  
37 middle-income countries (LMICs), which affects economically active populations and  
38 results in large economic impacts<sup>2</sup>.  
39

40 Evidence from randomized controlled trials (RCTs) demonstrated that anti-platelet  
41 therapy, ACE inhibitors/ARB, beta-blockers and statins are cost-effective in reducing the  
42 risk of ASCVD events in patients with established ASCVD, and these agents are included  
43 in the list of the World Health Organization (WHO) Essential Medicines List (EML)<sup>3</sup>.  
44 Treatment with these four proven medications (together with smoking cessation)  
45 prevents or postpones approximately 75-80% of recurrent vascular events and their  
46 complications, such as death and disability<sup>4</sup>.  
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49 Unfortunately, there is abundant evidence that the worldwide adherence to these  
50 cardiovascular medications in patients with ASCVD is far from ideal. Less than half of  
51 patients with known ASCVD disease in high-income countries are receiving this group  
52 of cardiovascular medications, and the situation is much worse in LMICs. The PURE  
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3 study showed that only 1 in 20 patients with ASCVD in LMICs are receiving the four types  
4 of cardiovascular drugs<sup>5</sup>.

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

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

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

50 A recent Cochrane review evaluated the effects of SMS on adherence to medications in  
51 patients with ASCVD<sup>12</sup>. The review identified seven trials (1310 participants) and showed  
52 a beneficial effect of SMS on adherence to medications in six of these trials. However,  
53 the quality of the evidence was very low. The Cochrane review identified the following  
54 limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a  
55 short follow-up (<6 months); (III) primary outcomes reported were of limited clinical  
56 relevance; (IV) most studies recruited only patients with acute coronary syndrome, which  
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3 leaves out an important group of patients with other arterial occlusive events (e.g.,  
4 ischaemic stroke, peripheral vascular disease and programmed coronary  
5 revascularizations) who should be amenable for this type of intervention; (V) few studies  
6 were performed in LMICs; and (VI) most trials did not describe the processes behind the  
7 SMS content generation, and the few trials that did report these processes did not target  
8 the key knowledge and attitudinal factors that are known to influence adherence to  
9 medication; instead the interventions were simple “reminders”.

10  
11 In conclusion, given the high prevalence of people with ASCVD in LMICs and the low  
12 use of cost-effective secondary prevention medications, a low-cost intervention that  
13 builds on a ubiquitous technology in LMICs, such as mobile phones, has the potential to  
14 improve public health. The current evidence shows that SMS interventions based on  
15 behaviour-change techniques are a potentially effective strategy to increase adherence  
16 to medications in people with ASCVD. However, further large trials are needed.

17  
18 To provide the high-quality evidence needed to assess the effect of SMS interventions  
19 based on behaviour-change techniques to increase adherence to medications in patients  
20 with ASCVD, we designed the txt2heart study, which is a large pragmatic superiority  
21 parallel randomized single-blind controlled trial with a 1:1 allocation ratio to evaluate the  
22 efficacy and safety of SMS on adherence to cardiovascular medications. The trial is  
23 being performed in a setting (Colombia) where patient factors, such as knowledge,  
24 attitudes and beliefs, are important determinants of adherence. In this context, medicines  
25 are widely available and generally affordable, so an intervention delivered to patients via  
26 SMS has the potential to be effective.

## 37 38 39 **METHODS AND ANALYSIS**

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42 This protocol is reported following the SPIRIT Standard Protocol Items recommendations  
43 for Interventional Trials<sup>13</sup> (see supplementary file 1).

### 44 45 46 **Aim and objectives**

47  
48 The primary objective is to evaluate the efficacy and safety of an intervention with  
49 SMS messages delivered by mobiles phones to improve adherence to  
50 cardiovascular medications in patients with atherosclerotic cardiovascular disease  
51 (ASCVD). We will assess the intervention efficacy via the measurement of blood  
52 serum LDL-C levels as an indicator of adherence to statins, systolic blood pressure as  
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3 an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart  
4 rate as an indicator of adherence to beta-blockers.  
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8 The secondary objective is to assess the impact of mobile text messaging on self-  
9 reported adherence to medications, hospitalizations, and the composite end-point of  
10 incident Major Adverse Cardiovascular Events (MACE) at 12 months.  
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### 13 14 **Choice of comparator**

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

34 Txt2heart Colombia is a two-parallel arm, single-blind individually randomized controlled  
35 trial. This design is aimed to minimize any potential bias that affects the internal validity  
36 of the study. The selection criteria were designed to increase the number of potential  
37 beneficiaries of the intervention and to keep the selection process as close as possible  
38 to the future scenario in which the intervention will be implemented. Therefore,  
39 Txt2Heart-Colombia is pragmatic in design. The active intervention will be the SMS  
40 delivered to mobile phones, and the content of the SMS is aimed to modify behaviours  
41 associated with poor adherence to ASCVD medications in ASCVD patients.  
42 Randomization will be performed as block randomization with a 1:1 allocation.  
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### 50 **Study setting**

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



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

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12 Exclusion criteria: Known contraindication to take all of the appropriate cardiovascular  
13 secondary prevention medications.  
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### 16 17 **Intervention**

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19 The intervention under evaluation consists of *behavioural change techniques* (BCTs)  
20 delivered via SMS. We developed our intervention following the recommendations of  
21 Abroms et al<sup>14</sup>. First, we reviewed the literature on individual level factors that influence  
22 adherence to medication. We performed country-specific qualitative studies using focus  
23 group discussions and semi-structured interviews to evaluate cardiovascular patients'  
24 perceptions about mHealth programmes to determine the necessary content and  
25 preferred timing and frequency of the SMS messages. To construct the content of the  
26 SMS, we wrote messages using educational and enabling behaviour change functions  
27 and established BCTs to target the potentially modifiable factors that influence the  
28 adherence referred to in the literature and found in our qualitative studies<sup>15</sup>. Finally, we  
29 tested the SMS messages with participants and adapted the messages based on their  
30 feedback to ensure the messages were understandable, acceptable, and relevant<sup>16</sup>. The  
31 resultant intervention delivered by SMS provides information about health consequences  
32 of adherence or non-adherence, instruction on how to take medication, medicine-taking  
33 prompts and cues, support in establishing medicine-taking habits, reframing medicine-  
34 taking and provides or encourages social support for taking medication<sup>17</sup>. The messages  
35 were designed according to the Transtheoretical Model (TTM) (Prochaska &  
36 DiClemente, 1992) and were aimed to enhance actions related to the steps and  
37 processes of this model. We will send messages daily the first month, three times per  
38 week the second month and once weekly the last ten months. This reducing frequency  
39 is consistent with the TTM, which suggests that people in the early stages of change  
40 require more intense input than people in later stages. In accordance with data from the  
41 focus groups, messages will be sent during working hours (08.00 – 18.00 hrs). The  
42 intervention will be delivered through an electronic platform, and it will be a one-way  
43 intervention. We will explain patients that they should not answer the messages, but they  
44 will be able to request to stop receiving the messages and withdraw from the trial by  
45 sending a message with the word "STOP". We will explain to patients that they should  
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3 send the 'stop' message in this situation. Stop messages will be saved and monitored  
4 by a trained engineer, separate from the study team, in order to maintain blinding.  
5 Similarly, a trained engineer, separate from the study team, will save and monitor the  
6 patients' answers if they respond to the messages. Because of the pragmatic nature of  
7 our study we will not tailor the messages. The trial intervention will start the day after  
8 recruitment and continue for 12 months or until the participant withdraws from the study  
9 or dies. The follow-up duration will be at least 12 months to a maximum of 36 months.  
10 Participants will not receive messages after month 12.  
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### 17 **Outcomes**

18 The primary outcome was selected for its clinical relevance and include: differences in  
19 changes (12 months "minus" baseline) in *Blood serum LDL-C levels* as an indicator of  
20 adherence to statins.  
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24 The following secondary outcomes will be included: *systolic blood pressure* as an  
25 indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs), *heart rate*  
26 as an indicator of adherence to beta-blockers, *urine levels of 11 dhTxB2* as an indicator  
27 of adherence to antiplatelet therapy; *self-reported adherence to cardiovascular*  
28 *medications* used in secondary prevention as measured using the MARS-5  
29 questionnaire; and rates of cardiovascular death or hospitalization due to cardiovascular  
30 disease and non-cardiovascular death or hospitalizations due to non-cardiovascular  
31 disease. We will also include road traffic crashes (the only potential known hazard of text  
32 messaging) and death due to all causes as secondary outcomes.  
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### 41 **Participant timeline**

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

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3 Randomization: We will use block randomization (varying size), stratifying by centre and  
4 with 1:1 allocation between the intervention and control arm. Randomization will be  
5 performed centrally using the CommCare platform after eligibility criteria was confirmed,  
6 informed consent signed, and baseline information collected. Therefore, the randomized  
7 allocation will not be revealed until after a participant was formally entered into the trial.  
8 Therefore, concealment of allocation will be complete. The SMS will be automatically  
9 generated by the CommCare platform and unknown to the investigators in contact with  
10 patients.  
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15 Blinding: Because of the nature of the intervention (SMS messages), it is not possible to  
16 include blind participants. However, the tx2heart trial will perform a blinded assessment  
17 of outcomes. Research personnel collecting data on clinical events, adherence scales,  
18 and biomarkers will not have access to treatment allocation. The laboratory results will  
19 be performed once trial follow-up is completed.  
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### 25 **Data collection methods**

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27 Txt2Heart Colombia will use Electronic Data Capture (EDC). These data will be entered  
28 in the CommCare platform, designed by Dimagi. CommCare is an open source mobile  
29 platform designed for data collection, client management, decision support, and  
30 behaviour change communication. The electronic devices (desktop computers, laptops  
31 and tablets) used in the trial are of exclusive use for the txt2Heart trial and owned by  
32 Fundación Cardiovascular de Colombia.  
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38 Our design aims to minimize the reactivity of assessment and the Hawthorne effect, while  
39 maximizing retention to follow-up. The following strategies to prevent loss to follow-up  
40 will be used. 1) One phone call at the third month of participation. Trained personnel  
41 different from the other interviewers will phone the participants to guarantee the blind  
42 design. Professionals in charge of the follow-up are trained in patient contact with the  
43 ability to empathize with volunteers. 2) We will register at least three relatives' numbers  
44 to contact in case we are not able to reach the patient, and we will phone the participant's  
45 relatives. 3) We will register the addresses of participants in case we cannot reach the  
46 patients or the relatives, and we will arrange a domiciliary visit. 4) We will share with the  
47 participants a contact phone number to let us to know if they change their phone number  
48 contact. We will explain these strategies to participants to get permission for further  
49 contact.  
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### 59 **Clinical outcomes**

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3 Death from cardiovascular causes and hospitalization due to nonfatal acute coronary  
4 syndrome, nonfatal stroke, or urgent revascularization will be defined by local  
5 investigators based on clinical notes and clear objective criteria using the suggestions  
6 provided by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular  
7 Endpoint Events in Clinical Trials<sup>18</sup>.  
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### 11 *Self-reported adherence*

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

25 In order to complete information about medications, we will ask patients about prescribed  
26 medication.  
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### 35 *Biomarkers*

36 Physiological measurements of heart rate and blood pressure will be measured using a  
37 calibrated Omron® device (Ref: HEM-7114) and Standard Operating Procedure by  
38 trained health care professionals. Patients will sit quietly for 10 minutes before the  
39 examinations.  
40

41 Blood LDL-C: Quantification of serum LDL will be performed using automated equipment  
42 by a direct method.  
43

44 Recent large epidemiological studies confirmed that resting heart rate is an independent  
45 predictor of cardiovascular mortality. Heart rate decrease is itself an important  
46 mechanism of the benefit of the blockers and other drugs that reduce heart rate after an  
47 acute myocardial infarction<sup>(1-4)</sup>. Controversies on the optimal dose to obtain results  
48 remain, but the reduction in heart rate is notorious in patients receiving beta-blockers<sup>5</sup>.  
49 In Colombia, beta-blockers are a first-line drug used for secondary prevention. The most  
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3 frequently beta-blocker is carvedilol, which exhibits advantages in decreasing heart rate  
4 and mortality in patients with some type of cardiovascular event<sup>6</sup>.  
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### 7 8 **Data management**

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

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

50 Data monitoring will be executed according to GCP Guidelines. This trial is a large,  
51 pragmatic, randomized controlled trial. The intervention is a strategy (SMS) to change  
52 behaviour and increase adherence of safe and proven effective interventions for  
53 secondary prevention that have been in clinical use for decades. Clinical management  
54 for underlying conditions will remain as per hospital's standard protocol. Based on these  
55 factors, the probability of harm or injury (physical, psychological, social or economic)  
56 occurring because of participation in this research study was assessed as low risk to  
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3 participants in each of these categories. Based on the low risks associated with this trial,  
4 there will not be a data monitoring committee. However, a monitoring plan to ensure  
5 appropriate performance of the trial will be developed, which will incorporate 100%  
6 central monitoring in conjunction with procedures, such as investigator training and  
7 meetings and written guidance. All data will be subject to statistical monitoring, and at  
8 least 10% of data will be subjected to on-site monitoring. Investigators/institutions are  
9 required to provide direct access to source data/documents for trial-related monitoring,  
10 audits, ethics committee review and regulatory inspection. All trial-related and source  
11 documents must be kept for 15 years after the end of the trial.  
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### 19 **Patient and Public Involvement**

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

#### 34 **Protocol amendments**

35 We redefined systolic blood pressure and heart rate as secondary outcomes because  
36 we do not have calculation power for these measures. In the first version of protocol,  
37 these measures were primary outcomes.  
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#### 42 **Ethical considerations**

43 The study will be performed in compliance with the protocol, regulatory requirements,  
44 GCP and the ethical principles of the Declaration of Helsinki.  
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#### 49 **Ethical approval**

50 The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and  
51 approved the trial.  
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#### 55 **Informed Consent:**

56 The investigator or designated personnel will inform the patient of the objectives,  
57 methods, anticipated benefits and potential risks and inconveniences of the study. The  
58 patient will be given every opportunity to clarify any points he/she does not understand  
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3 and, if necessary, ask for more information. Written consent must be given by the patient  
4 and/or the legal guardian of the patient after detailed information about the study is  
5 provided in accordance with any national provisions on the protection of clinical study  
6 patients. The verbal explanation will cover all of the elements specified in the written  
7 information provided to the patient. Patients and/or legal guardians will be required to  
8 sign and date the informed consent form. Patients who refuse to give or who withdraw  
9 written informed consent will not be included or continue in the study. The trial will include  
10 a "Pre-selection" Informed Consent, per law 1581 of 2012 and decree 1377 of 2013 or  
11 law of protection of personal data, where the study team is authorized to handle personal  
12 and clinical data of the subject. Calls made in the pre-selection and phase 2 visit will be  
13 recorded and stored for a set time. Eligible participants will only be included in the study  
14 after signing "Txt2Heart-Colombia" informed consent (testified, where required by law or  
15 regulation), as approved by the ethics committees. The process will be documented in  
16 the patient source documents, specifically in CRFs (Case Report Form).  
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27 Confidentiality: Information about the study subjects will be kept confidential. The  
28 investigators will ensure the anonymity of patients, and patients will not be identified by  
29 name in any document. Informed consent forms and patient recruitment registration will  
30 be kept strictly confidential only to permit identification of the patient at Fundación  
31 Cardiovascular de Colombia. Information about the study subjects will be handled under  
32 the laws and regulations of Colombia (Law 1581 of 2012 and Decree 1377 of 2013, Law  
33 of data protection). The regulations that require an authorization signed by the patient  
34 including the follow information: What protected health information (PHI) will be collected  
35 from the study subjects, who will have access to that information and why, who will use  
36 and disclose that information and the right to withdraw his/her authorization to use their  
37 PHI.  
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#### 46 **Access to data**

47 The principal investigator and sub-investigators will have access to the data to verify and  
48 analyse the results. To ensure confidentiality, all of the investigators will be blinded of  
49 participant identification.  
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#### 53 **Ancillary and post-trial care**

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

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11 The Txt2heart Colombia trial is aimed to provide high level evidence that evaluates  
12 whether SMS messages delivered through mobile telephones change the behaviour of  
13 Colombian patients who have suffered a cardiovascular event. Trial results will be  
14 presented to the health local authorities, and if the intervention is effective and safe, we  
15 hope this strategy will be implemented quickly because of its low cost and wide-reaching  
16 impact on the population.  
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22 The results from the trial will be published in an open journal to provide scientists,  
23 clinicians and policymakers access to the data.  
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### 26 **Limitations**

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

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5 *Principal investigator*  
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8 Anderson Bermon, MD, MSc: associate researcher and epidemiologist at Fundación  
9 Cardiovascular de Colombia, Demography and Biostatistics PhD student at CES  
10 University. Dr. Bermon participated in the trial design and studied the impact of the  
11 results in Colombia, considering the healthcare system limitations.  
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14

15 Ana Fernanda Uribe Rodríguez, PhD: Senior researcher and Associate Professor  
16 Faculty of Psychology, Pontificia Bolivariana University. Dr. Uribe designed the message  
17 intervention and studied the behavioural theories that support the intervention  
18 methodology.  
19  
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23 *Study chair*  
24

25  
26 Juan P. Casas, PhD: Professor in Clinical Epidemiology and Informatics at University  
27 College London at Massachusetts Veterans Epidemiology Research and Information  
28 Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. Dr. Casas  
29 conceived the idea of conducting the trial and participated in the methodology design of  
30 the trial.  
31  
32  
33  
34

35  
36 Pablo A Perel, PhD: Professor in Clinical Epidemiology Faculty of Epidemiology &  
37 Population Health London School of Hygiene & Tropical Medicine. Dr. Perel conceived  
38 the idea of conducting the trial and participated in the methodology design of the trial.  
39  
40  
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42

43 *Sub-investigators:*  
44

45 Elizabeth Murray, PhD: Professor of eHealth and Primary Care at the Research  
46 Department of Primary Care and Population Health, University College London. Dr.  
47 Murray contributed in the intervention design and message validity process.  
48  
49  
50

51 David Prieto-Merino, PhD: Associate Professor Faculty of Epidemiology & Population  
52 Health London School of Hygiene & Tropical Medicine. Dr. Prieto-Merino designed the  
53 statistical analysis and data management of the trial.  
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2  
3 Caroline Free: Associate Professor Faculty of Epidemiology & Population Health London  
4 School of Hygiene & Tropical Medicine. Dr. Free conceived the idea of conducting and  
5 participated in the validity process of the message intervention.  
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7

8  
9 Lou Atkins, PhD: Senior Teaching Fellow at University College London. Dr. Atkins  
10 contributed in the message intervention design.  
11  
12

13  
14 Robert Horne, PhD: Director, Centre for Behavioural Medicine, UCL School of  
15 Pharmacy, University College London. Dr. Horne participated in the validity process of  
16 the message intervention and choosing adherence scales.  
17  
18

19  
20 Elizabeth Guio, MSc: Metabolism and Genome Laboratory director at Fundación  
21 Cardiovascular de Colombia. Dr. Guio participated in choosing the biomarkers and the  
22 processing design for biological samples.  
23  
24

25  
26 Diana Isabel Cáceres Rivera, PhD: Associate Professor Faculty of Nursing at  
27 Cooperativa Colombia University. Dr. Cáceres contributed to the trial design.  
28  
29

30  
31 Paula Fernanda Pérez Rivero: COLCIENCIAS Young researcher and assistant  
32 researcher at Pontificia Bolivariana University. As young researcher, Psy. Pérez  
33 participated in the intervention design.  
34  
35

### 36 37 38 **Acknowledgments statement**

39  
40 We thank the Cardiology Department medical staff at Fundación Cardiovascular de  
41 Colombia for their help with developing our research questions.  
42  
43

### 44 45 **Funding statement**

46  
47 This work was supported by COLCIENCIAS code 656672553352 grant 899-2015  
48  
49 Fundación Cardiovascular de Colombia, Floridablanca  
50 London School of Hygiene and Tropical Medicine, UK Medical Research Council Funded  
51 Reference MR/N021304/1  
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53 Universidad Pontificia Bolivariana, Bucaramanga sectional  
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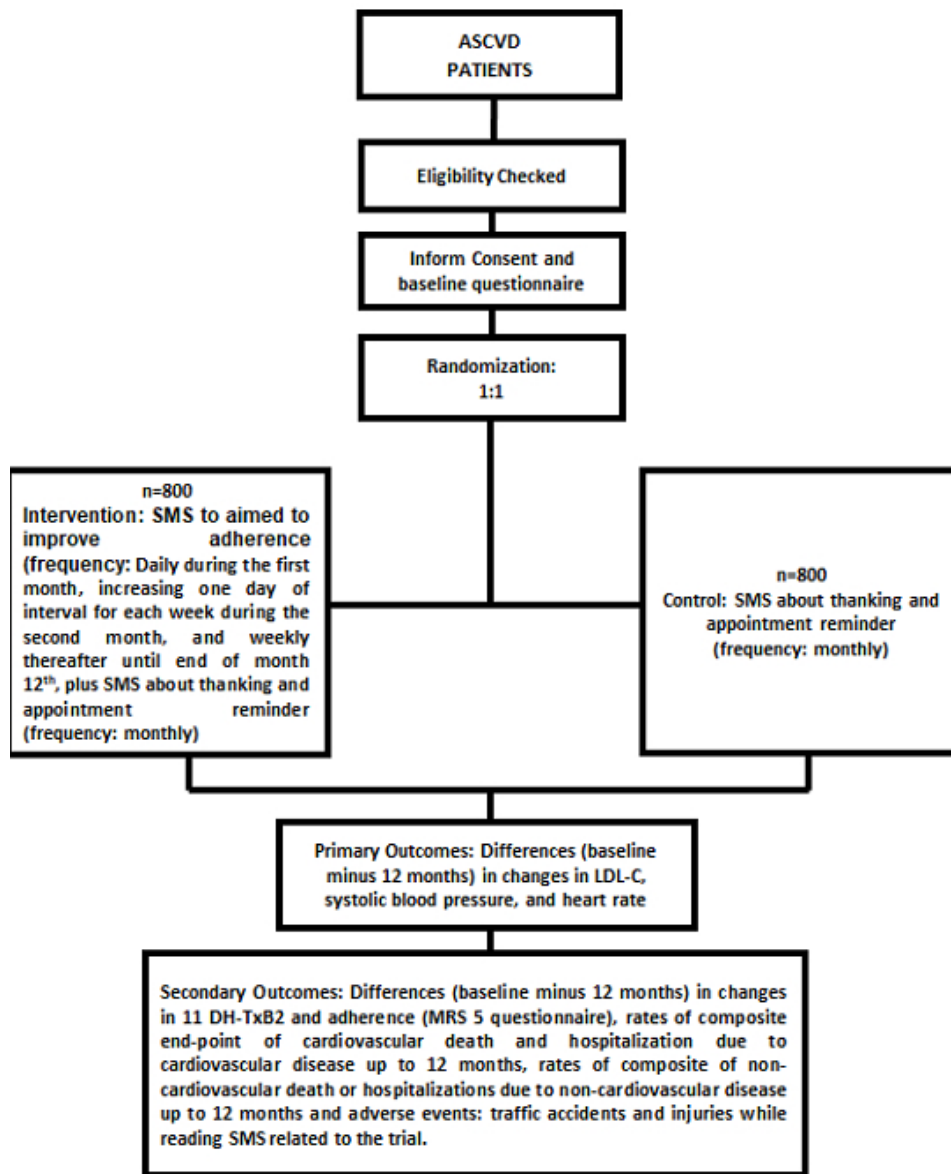
### 58 **Competing interests' statement**

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60 All authors declare there is not conflict of interest.

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All funding institutions declare there is not conflict of interest.

For peer review only



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: <a href="mailto:contacto@colciencias.gov.co">contacto@colciencias.gov.co</a> (+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	<p>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.</p> <p>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.</p>
Key inclusion and exclusion criteria	<p>Inclusion Criteria:</p> <p>Age <math>\geq 18</math> years old</p> <p>Sexes eligible for study: both</p> <p>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).</p> <p>Own at least one mobile phone</p>

	<p>Ability to read and understand text messages (SMS)</p> <p>Intention to stay in the country of recruitment during the next 12 months</p> <p>Exclusion Criteria:</p> <p>Contraindication to take all cardiovascular medications used in secondary prevention.</p> <p>Participation in another randomized clinical trial that could interfere with adherence to treatment.</p>
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)	<p>Differences in changes (baseline minus 12 months) of:</p> <p>Low density lipoprotein cholesterol (LDL-C)</p> <p>Systolic Blood pressure</p> <p>Heart Rate</p>
Key secondary outcomes	<p>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.</p> <p>Rates of composite end-point of cardiovascular death and hospitalization due to cardiovascular disease up to 12 months.</p> <p>Rates of composite of non-cardiovascular death or hospitalizations due to non-cardiovascular disease up to 12 months</p> <p>Adverse events: traffic accidents and injuries while reading SMS related to the trial.</p>

# 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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	2
2				
3	data set		Registration Data Set	
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6	Protocol version	<a href="#">#3</a>	Date and version identifier	15
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9				
10	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	20
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12				
13	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	18
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15	responsibilities:			
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17	contributorship			
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20	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	2
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22	responsibilities:			
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24	sponsor contact			
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26	information			
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30	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	18
31				
32	responsibilities:		collection, management, analysis, and interpretation of	
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34	sponsor and funder		data; writing of the report; and the decision to submit the	
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42	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	18
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44	responsibilities:		centre, steering committee, endpoint adjudication	
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46	committees		committee, data management team, and other individuals or	
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54	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
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56	rationale		undertaking the trial, including summary of relevant studies	
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1		(published and unpublished) examining benefits and harms	
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3		for each intervention	
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6	Background and	<a href="#">#6b</a> Explanation for choice of comparators	7
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8	rationale: choice of		
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10	comparators		
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12			
13	Objectives	<a href="#">#7</a> Specific objectives or hypotheses	7
14			
15			
16	Trial design	<a href="#">#8</a> Description of trial design including type of trial (eg, parallel	7
17		group, crossover, factorial, single group), allocation ratio,	
18		and framework (eg, superiority, equivalence, non-inferiority,	
19		exploratory)	
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26	Study setting	<a href="#">#9</a> Description of study settings (eg, community clinic,	8
27		academic hospital) and list of countries where data will be	
28		collected. Reference to where list of study sites can be	
29		obtained	
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43	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If applicable,	8
44		eligibility criteria for study centres and individuals who will	
45		perform the interventions (eg, surgeons, psychotherapists)	
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51	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	8
52		replication, including how and when they will be	
53	description	administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	9
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	10
12				
13	adherence		and any procedures for monitoring adherence (eg, drug	
14			tablet return; laboratory tests)	
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19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	8
20				
21	concomitant care		permitted or prohibited during the trial	
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23				
24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	13
25			specific measurement variable (eg, systolic blood pressure),	
26			analysis metric (eg, change from baseline, final value, time	
27			to event), method of aggregation (eg, median, proportion),	
28			and time point for each outcome. Explanation of the clinical	
29			relevance of chosen efficacy and harm outcomes is strongly	
30			recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	9
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly recommended	
44			(see Figure)	
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study	11
52			objectives and how it was determined, including clinical and	
53			statistical assumptions supporting any sample size	
54			calculations	
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to	11
2			reach target sample size	
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6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	12
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a random	
9			sequence, details of any planned restriction (eg, blocking)	
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11			should be provided in a separate document that is	
12			unavailable to those who enrol participants or assign	
13			interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,	12
24	concealment		central telephone; sequentially numbered, opaque, sealed	
25			envelopes), describing any steps to conceal the sequence	
26	mechanism		until interventions are assigned	
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	12
34	implementation		participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	12
42			trial participants, care providers, outcome assessors, data	
43			analysts), and how	
44				
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48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	12
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
51	unblinding			
52				
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56	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	13
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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

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15	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow- 13
16			
17	retention		up, including list of any outcome data to be collected for
18			participants who discontinue or deviate from intervention
19			protocols
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25	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including 14
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27			any related processes to promote data quality (eg, double
28			data entry; range checks for data values). Reference to
29			where details of data management procedures can be
30			found, if not in the protocol
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37	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary 14
38			
39			outcomes. Reference to where other details of the statistical
40			analysis plan can be found, if not in the protocol
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45	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and 14
46			
47	analyses		adjusted analyses)
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49			
50	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non- 14
51			
52	population and		adherence (eg, as randomised analysis), and any statistical
53			methods to handle missing data (eg, multiple imputation)
54	missing data		
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58	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary 15
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1	formal committee		of its role and reporting structure; statement of whether it is	
2			independent from the sponsor and competing interests; and	
3			reference to where further details about its charter can be	
4			found, if not in the protocol. Alternatively, an explanation of	
5			why a DMC is not needed	
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12	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	15
13	interim analysis		including who will have access to these interim results and	
14			make the final decision to terminate the trial	
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20	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	17
21			solicited and spontaneously reported adverse events and	
22			other unintended effects of trial interventions or trial conduct	
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28	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any,	15
29			and whether the process will be independent from	
30			investigators and the sponsor	
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35	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional	15
36	approval		review board (REC / IRB) approval	
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41	Protocol	<a href="#">#25</a>	Plans for communicating important protocol modifications	15
42	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
43			relevant parties (eg, investigators, REC / IRBs, trial	
44			participants, trial registries, journals, regulators)	
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51	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential	16
52			trial participants or authorised surrogates, and how (see	
53			Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	16
2				
3	ancillary studies		participant data and biological specimens in ancillary	
4			studies, if applicable	
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8	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	16
9			participants will be collected, shared, and maintained in	
10			order to protect confidentiality before, during, and after the	
11			trial	
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18	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	16
19	interests		investigators for the overall trial and each study site	
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24	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	16
25			and disclosure of contractual agreements that limit such	
26			access for investigators	
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31	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	16
32	trial care		compensation to those who suffer harm from trial	
33			participation	
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39	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	17
40	trial results		results to participants, healthcare professionals, the public,	
41			and other relevant groups (eg, via publication, reporting in	
42			results databases, or other data sharing arrangements),	
43			including any publication restrictions	
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51	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	17
52	authorship		professional writers	
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57	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	17
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1	reproducible	participant-level dataset, and statistical code	
2			
3	research		
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6	Informed consent	<a href="#">#32</a> Model consent form and other related documentation given	16
7			
8	materials	to participants and authorised surrogates	
9			
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11	Biological specimens	<a href="#">#33</a> Plans for collection, laboratory evaluation, and storage of	13
12			
13		biological specimens for genetic or molecular analysis in the	
14			
15		current trial and for future use in ancillary studies, if	
16			
17		applicable	
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23 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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