PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Text messaging support for patients with diabetes or coronary artery disease (SupportMe): Protocol for a pragmatic randomised controlled trial
AUTHORS	Cheung, N Wah; Redfern, Julie; Thiagalingam, Aravinda; Hng, Tien-Ming; Shariful Islam, Sheikh Mohammed; Haider, Rabbia; Faruquie, Sonia; Chow, Clara

VERSION 1 - REVIEW

REVIEWER	Lixin Jiang National Center for Cardiovascular Diseases. Fuwai Hospital, China
REVIEW RETURNED	28-Aug-2018

GENERAL COMMENTS	This program is developed based on the framework of TextMe and the protocol is well written. Just two questions: 1 Generally speaking, the primary endpoint is the main hypothesis we want to test in a trial. In this protocol, the primary endpoint is the change of blood pressure at 6 months. What's the rationale for this? Why this is important? Will the intervention lead to the improvement in SBP change? It needs to be addressed in Introduction. Why not select a composite endpoint as the primary endpoint? 2 For the inclusion criteria of study population, the participants needed to be those with hypertension or with uncontrolled hypertension? Or any patients with CAD/DM will be eligible? What's the relevant rationale?

REVIEWER	Jeremy Sussman University of Michigan and VA Ann Arbor, USA
REVIEW RETURNED	16-Nov-2018

GENERAL COMMENTS	Excellent study with a clearly-written and conceived design. I am surprised the authors didn't have any restrictions on baseline BP or A1c as an inclusion criteria. If baseline BP is well-controlled, this could dramatically alter the study's power. (This team is clearly aware of issues like that. I'm mostly curious what their reasoning was, though I assume it's for easier enrollment.)

REVIEWER	Professor Stephen Walters University of Sheffield United Kingdom
REVIEW RETURNED	17-Dec-2018

GENERAL COMMENTS	"Text messaging support for patients with diabetes or coronary artery disease (SupportMe): Protocol for a pragmatic randomised controlled trial" for BMJ Open. There appears to be inconsistencies between the BMJ Open protocol paper that has been submitted and the more detailed protocol. These should be corrected. Need to be clear what the primary outcome is. The paper and protocol say different things. Is the primary outcome systolic blood pressure at six months' post-randomisation (as specified in the protocol)? Or is the is the primary outcome the change systolic blood pressure between baseline and six months' post-randomisation (as specified in the submitted protocol paper)? Abstract needs to make clear the primary outcome is the change in systolic blood pressure from baseline to six-months post-randomisation. Randomisation No need to specify block size, of 8, in randomisation description. Sample size The sample size estimate of N= 1000 participants seems sensible. I cannot replicate the sample size, given the parameters stated in the protocol paper. Sufficient information needs to be reported in the protocol to replicate the sample. The standard deviation of the outcome needs to be reported. It is reported in the detailed protocol as 17 mmHg but not in the protocol paper. If the primary outcome is the change in blood pressure from baseline to six-months post randomisation, then the SD of the change in BP from baseline to six months needs to reported. Target difference in blood pressure: 2.5 or 3.5 mmHg? The target difference used in the sample size calculation needs to be justified as per the DELTA2 guidance. Also the protocol paper says a target difference of 2.5 mmHg whilst the protocol says 3.5mmHG? What target difference in SBS are the investigators looking for? Are differences of this magnitude likely to be of any clinical or practical importance? Cook JA et al (2018) DELTA² guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. BMJ (Online), 363. The investigators have made no allowance in the sample size calculation for attrition or loss to follow-up. A recent survey of UK publicly funded trials suggests an average attrition of at least 10%. Walters SJ et al (2017) Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open, 7(3). Statistical Analysis Plan The statistical analysis is under specified and lacks basic details. There is no mention of CONSORT for reporting of the results of the study: there should be.

	The paper states “The study will follow the intention-to-treat principle for analyses and participants will be analysed at 6 months by original assigned groups. Baseline comparisons between groups will be undertaken by independent t-tests or Mann-Whitney tests for continuous variables and chi square tests for categorical variables.” CONSORT 2010 says “Tests of baseline differences are not necessarily wrong, just illogical.211 Such hypothesis testing is superfluous and can mislead investigators and their readers. Rather, comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred.211” Sen S. Testing for baseline balance in clinical trials. Stat Med. 1994 Sep 15;13(17):1715-26. Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate. Michiel R de Boer et al E International Journal of Behavioral Nutrition and Physical Activity201512:4 https://doi.org/10.1186/s12966-015-0162-z There is no mention of estimation of confidence intervals (CIs) for the treatment difference as per CONSORT. The applicants should justify why they are using the change (CHANGE) in BP from randomisation to 6-month follow-up; rather than follow-up or post-treatment BP (POST) adjusted for baseline score? Since you have an RCT design then randomisation of the participants should ensure that all have similar baseline levels of the outcome. In these circumstances it is well known (Frison and Pocock, 1992) that the most powerful method of statistical analysis of the outcome data is ANCOVA (i.e. post-treatment score adjusted for baseline score and treatment group) rather than analysis of change from baseline scores (CHANGE) or comparison of post-treatment means (POST). Frison L. & Pocock S.J. Repeated Measures in Clinical Trials: Analysis Using Mean Summary Statistics and Its Implications for Design. Statistics in Medicine 1992; 11: 1685-1704. Missing data; there is no mention of how missing primary outcome data is to be handled. What about imputation of missing data? Will the diabetes only; diabetes and CAD, and CAD only groups of patients be analysed separately or combined? The protocol paper is not clear. The protocol paper mentions subgroups: “Heterogeneity of treatment on the primary endpoint will be assessed in pre-defined subgroups of baseline values for BP, BMI, LDL-cholesterol, HbA1c, and background BP lowering therapy, ethnicity, age, gender, participation in the WSICP, and medical conditions.” Any subgroup analyses should be based on an interaction statistical test between the randomised intervention group and subgroup to directly examine the strength of evidence for the treatment difference between the treatment groups varying between subgroups. Carer involvement (yes or no) will be the only a priori defined sub groups to be considered for interaction test. Sub group analysis will be performed regardless of the statistical significance on the overall intervention effect.

	The protocol Table 1 seems to imply that trial participants will be follow-up for up to 2 years' post-randomisation. What about the analysis and reporting of longer term outcomes? The repeated outcome assessments, post-randomisation, need to be analysed by either creating a summary measure such as the mean score post randomisation or AUC; or using a longitudinal model. Also it appears that control participants can "cross over" at the end of six months to receive the intervention. How will this longer term outcome data be analysed? "At the end of the 6-month program, maintenance messages will be sent to intervention subjects for a further 6 months at a frequency of 2 per week. Control subjects will be offered the opportunity to receive the SupportMe intervention at that point." The reporting of Serious Adverse events should be clearly described. Table 1 Schedule of events in the protocol should be included in the protocol paper. The trial management arrangements e.g. TMG; TSC and DMEC appear to be satisfactory. Does the DMEC need an independent statistician?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Lixin Jiang

Institution and Country: National Center for Cardiovascular Diseases. Fuwai Hospital, China

Please state any competing interests or state 'None declared': No.

Please leave your comments for the authors below This program is developed based on the framework of TextMe and the protocol is well written. Just two questions:

1 Generally speaking, the primary endpoint is the main hypothesis we want to test in a trial. In this protocol, the primary endpoint is the change of blood pressure at 6 months. What's the rationale for this? Why this is important? Will the intervention lead to the improvement in SBP change? It needs to be addressed in Introduction. Why not select a composite endpoint as the primary endpoint?

As our trial has 2 subgroups, those with coronary artery disease, and those with type 2 diabetes, the primary outcome needed to be an outcome which is important to both groups of patients. Blood pressure control is important to both subgroups, and there are clear guidelines for both. We have shown in a similar study for patients with coronary artery disease, that even with reasonable BP at baseline, the intervention results in a relative improvement in BP (Chow et al, JAMA 2015; 314: 1255-63). For subjects with diabetes, Australian data (including local data) indicates that BP is often higher

than desirable and targets are seldom achieved (Cheung et al, Diabetic Med 2008; 25: 974-78 and Lam et al, Diabetes Res Clin Pract 2016; 116: 159-64).

We have now included these sentences in the introduction. “Hypertension is one risk factor common to both people with CVD and type 2 diabetes that is often inadequately managed. We have previously shown that without support, blood pressure amongst patients with coronary artery disease deteriorates following discharge from hospital cardiac services (Chow, JAMA). Even patients with diabetes who attend specialist practices often have elevated blood pressure and fail to meet guideline targets (Cheung, DM, Lam DRCP).”

Later in the introduction we have also now emphasised blood pressure as an outcome. “The intervention will provide education, clinical management support and healthy lifestyle motivation, with the aim of improving cardiovascular risk factors, in particular blood pressure, and diabetes care.”

2 For the inclusion criteria of study population, the participants needed to be those with hypertension or with uncontrolled hypertension? Or any patients with CAD/DM will be eligible? What’s the relevant rationale?

We did not stipulate an exclusion or inclusion criterion based on blood pressure. Our experience is that most patients do not meet BP targets and there is potential for improvement. In our previous study of patients with coronary artery disease, we found that blood pressure amongst unsupported patients deteriorated over time even if it was reasonable at baseline. Any patient with CAD (defined as history of prior myocardial infarction or documented >50% of major coronary artery on invasive or non-invasive coronary angiography) or type 2 diabetes (with HbA1c 7.1-11.4% (54-101 mmol/mol)) was eligible, providing they met age and technical requirements. For the rationale see response to Q1.

Reviewer: 2

Reviewer Name: Jeremy Sussman

Institution and Country: University of Michigan and VA Ann Arbor, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Excellent study with a clearly-written and conceived design.

I am surprised the authors didn't have any restrictions on baseline BP or A1c as an inclusion criteria. If baseline BP is well-controlled, this could dramatically alter the study's power. (This team is clearly aware of issues like that. I'm mostly curious what their reasoning was, though I assume it's for easier enrollment.)

We did not have restrictions on blood pressure for recruitment as our experience and local data indicate that blood pressure is often not well controlled amongst people with diabetes and targets are not met (Cheung et al, Diabetic Med 2008; 25: 974-78 and Lam et al, Diabetes Res Clin Pract 2016; 116: 159-64). In our previous study of patients with coronary artery disease, we found that blood pressure amongst unsupported patients deteriorated over time even if it was reasonable at baseline.

We have added in these sentences in the introduction: ”We have previously shown that without support, blood pressure control deteriorates amongst patients with coronary artery disease following discharge from hospital cardiac services (Chow, JAMA). Even patients with diabetes who attend specialist practices often have elevated blood pressure and fail to meet guideline targets (Cheung, DM, Lam DRCP).”

We do have an HbA1c restriction of 7.1-11.4% (54-101 mmol/mol). This is stated in the Methods, page 7.

Reviewer: 3

Reviewer Name: Professor Stephen Walters

Institution and Country: University of Sheffield, United Kingdom

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below "Text messaging support for patients with diabetes or coronary artery disease (SupportMe): Protocol for a pragmatic randomised controlled trial" for BMJ Open.

There appears to be inconsistencies between the BMJ Open protocol paper that has been submitted and the more detailed protocol. These should be corrected.

There are a number of existing discrepancies for which we have not put in formal amendments to date. Following the revision of the protocol paper, we will submit an amendment to ethics and the trial registry which covers all the protocol changes.

Need to be clear what the primary outcome is. The paper and protocol say different things. Is the primary outcome systolic blood pressure at six months’ post-randomisation (as specified in the protocol)? Or is the is the primary outcome the change systolic blood pressure between baseline and six months’ post-randomisation (as specified in the submitted protocol paper)?

Apologies, the primary outcome is systolic blood pressure at 6 months, as per the protocol. We have modified our text under Study Outcomes to make this clear: “The primary outcome of the study is systolic blood pressure after 6 months.”

Abstract needs to make clear the primary outcome is the change in systolic blood pressure from baseline to six-months post-randomisation.

We now state in the abstract “The primary outcome is the systolic blood pressure at 6 months.”, rather than change in blood pressure (as per previous query and response).

Randomisation

No need to specify block size, of 8, in randomisation description.

We have now deleted this.

Sample size

The sample size estimate of N= 1000 participants seems sensible. I cannot replicate the sample size, given the parameters stated in the protocol paper. Sufficient information needs to be reported in the protocol to replicate the sample. The standard deviation of the outcome needs to be reported. It is reported in the detailed protocol as 17 mmHg but not in the protocol paper.

If the primary outcome is the change in blood pressure from baseline to six-months post randomisation, then the SD of the change in BP from baseline to six months needs to reported.

Target difference in blood pressure: 2.5 or 3.5 mmHg?

The target difference used in the sample size calculation needs to be justified as per the DELTA2 guidance. Also the protocol paper says a target difference of 2.5 mmHg whilst the protocol says 3.5mmHG? What target difference in SBS are the investigators looking for? Are differences of this magnitude likely to be of any clinical or practical importance?

Cook JA et al (2018) DELTA² guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. BMJ (Online), 363.

The investigators have made no allowance in the sample size calculation for attrition or loss to follow-up. A recent survey of UK publicly funded trials suggests an average attrition of at least 10%.

Walters SJ et al (2017) Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open, 7(3).

Since the original submission of this protocol paper, we have developed a formal statistical analysis plan and reconciled our discrepancies. The Statistical Analyses section of the paper now reads:

“We plan to recruit 1000 subjects into the study, with at least 500 patients with each of diabetes or CHD. A sample of 1000 subjects will enable detection of a 3.5 mmHg difference in sBP with 90% power and no loss to follow up (Type 1 error 5%, 2 sided alpha and assuming a conservative standard deviation (SD) of 17) and 80% power if there was approximately 20% loss to follow-up. If the SD of 12mmHg from our earlier TEXT ME study18 was applied, a sample size of 720 subjects has 90% power to detect a difference of 2.5 mmHg with no loss to follow-up, but with 20% loss to follow-up, 900 subjects would be required. Within the strata of diabetes or CHD, a sample size of 500 and accounting for 20% loss to follow-up, would have 80% power to detect a 5 mmHg difference in sBP (SD 17 mmHg) and 80% power to detect a 3.5 mmHg difference assuming a SD of 12 mmHg. Data from the Blood Pressure Lowering Treatment Trialist’s Collaboration indicate that a reduction in BP of 5 mmHg reduces the risk of major cardiovascular events, irrespective of the form of pharmacotherapy26. We also planned for an adequate sample size to demonstrate an improvement in diabetes control, as measured by HbA1c. Applying local data regarding the distribution of HbA1c27, a sample size of 500 without loss to follow-up is required for 80% power to detect a difference of 0.3% in HbA1c in the diabetes cohort (SD=1.2), but if allowing for 20% drop-out, the required sample size increases to 625. This quantum of HbA1c reduction translates to a 6% reduction in risk of diabetes complications28. As we expect >20% of CHD patients to also have diabetes, there will be at least 600 patients with diabetes in the total 1000 subject cohort.

The study will follow intention-to-treat principles for analyses. Participants will be analysed at 6 months by original assigned groups. The primary analysis will use analysis of covariance (ANCOVA) adjusting for baseline sBP. To explore the treatment effect by prespecified risk factors, namely baseline high/low BP, BMI groupings, high/normal LDL-cholesterol, high/normal HbA1c, whether they had background BP lowering therapy, ethnicity group, age groups, gender, participation in WSICP and medical conditions, a model of 6 month sBP will be performed adjusting for baseline sBP, treatment, risk factors and the interaction of each risk factor with treatment. The modelled mean differences with 95% confidence intervals for each risk factor will be presented in a forest plot together with tests of interaction to assess whether the treatment effect varies between levels of each risk factor.

The pattern of missing data for the primary and subgroup analysis will be explored to assess if some baseline characteristics predict missing sBP or HbA1c at 6 months using a log binomial regression analysis. The study will be reported following CONSORT2010 guidelines30.”

Statistical Analysis Plan

The statistical analysis is under specified and lacks basic details. There is no mention of CONSORT for reporting of the results of the study: there should be.

The paper states “The study will follow the intention-to-treat principle for analyses and participants will be analysed at 6 months by original assigned groups. Baseline comparisons between groups will be undertaken by independent t-tests or Mann-Whitney tests for continuous variables and chi square tests for categorical variables.”

CONSORT 2010 says

“Tests of baseline differences are not necessarily wrong, just illogical.211 Such hypothesis testing is superfluous and can mislead investigators and their readers. Rather, comparisons at baseline should

be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred.211”

Sen S. Testing for baseline balance in clinical trials.

Stat Med. 1994 Sep 15;13(17):1715-26.

Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate. Michiel R de Boer et al E

International Journal of Behavioral Nutrition and Physical Activity201512:4 https://protect-au.mimecast.com/s/MUUvCANZvPi5qqZPcGKvu3?domain=doi.org

It is our intention to report baseline parameters for the purpose of describing the cohort only. We will be analysing the outcomes by ANCOVA which will factor in the relative importance of any baseline differences. To avoid misleading readers, we have now deleted the sentence regarding baseline comparisons.

We now state that “The study will be reported following CONSORT2010 guidelines“

There is no mention of estimation of confidence intervals (CIs) for the treatment difference as per CONSORT.

The applicants should justify why they are using the change (CHANGE) in BP from randomisation to 6-month follow-up; rather than follow-up or post-treatment BP (POST) adjusted for baseline score? Since you have an RCT design then randomisation of the participants should ensure that all have similar baseline levels of the outcome. In these circumstances it is well known (Frison and Pocock, 1992) that the most powerful method of statistical analysis of the outcome data is ANCOVA (i.e. post-treatment score adjusted for baseline score and treatment group) rather than analysis of change from baseline scores (CHANGE) or comparison of post-treatment means (POST).

Frison L. & Pocock S.J. Repeated Measures in Clinical Trials: Analysis Using Mean Summary Statistics and Its Implications for Design. Statistics in Medicine 1992; 11: 1685-1704.

To respond to this query, we need to clarify that the primary outcome is not change in BP, and is in fact systolic BP at 6 months. We have modified the following paragraph: “The study will follow intention-to-treat principles for analyses. Participants will be analysed at 6 months by original assigned groups. The primary analysis will use analysis of covariance (ANCOVA) adjusting for baseline sBP. To explore the treatment effect by prespecified risk factors, namely baseline high/low BP, BMI groupings, high/normal LDL-cholesterol, high/normal HbA1c, whether they had background BP lowering therapy, ethnicity group, age groups, gender, participation in WSICP and medical conditions, a model of 6 month sBP will be performed adjusting for baseline sBP, treatment, risk factors and the interaction of each risk factor with treatment. The modelled mean differences with 95% confidence intervals for each risk factor will be presented in a forest plot together with tests of interaction to assess whether the treatment effect varies between levels of each risk factor.”

Missing data; there is no mention of how missing primary outcome data is to be handled. What about imputation of missing data?

A potential drop out of 20% is anticipated. Imputation of missing values is not meaningful in our trial given that we only have measures at baseline and 6 months. We now indicate that “The pattern of missing data for the primary and subgroup analysis will be explored to assess if some baseline characteristics predict missing sBP or HbA1c at 6 months using a log binomial regression analysis.”

Will the diabetes only; diabetes and CAD, and CAD only groups of patients be analysed separately or combined? The protocol paper is not clear.

The protocol paper mentions subgroups:

“Heterogeneity of treatment on the primary endpoint will be assessed in pre-defined subgroups of baseline values for BP, BMI, LDL-cholesterol, HbA1c, and background BP lowering therapy, ethnicity, age, gender, participation in the WSICP, and medical conditions.”

Any subgroup analyses should be based on an interaction statistical test between the randomised intervention group and subgroup to directly examine the strength of evidence for the treatment difference between the treatment groups varying between subgroups. Carer involvement (yes or no) will be the only a priori defined sub groups to be considered for interaction test. Sub group analysis will be performed regardless of the statistical significance on the overall intervention effect.

Apologies for our loose terminology. The only subgroups are those with coronary heart disease, and those with type 2 diabetes. The main analysis is based on the entire cohort. However we will also analyse the effect of the intervention in each of these 2 subgroups, in particular HbA1c amongst those with diabetes.

What we had called “pre-defined subgroups” are more appropriately defined as “prespecified risk factors. We have modified the sentence as such: “To explore the treatment effect by prespecified risk factors, namely baseline high/low BP, BMI groupings, high/normal LDL-cholesterol, high/normal HbA1c, whether they had background BP lowering therapy, ethnicity group, age groups, gender, participation in WSICP and medical conditions, a model of 6 month sBP will be performed adjusting for baseline sBP, treatment, risk factors and the interaction of each risk factor with treatment. The modelled mean differences with 95% confidence intervals for each risk factor will be presented in a forest plot together with tests of interaction to assess whether the treatment effect varies between levels of each risk factor.”

The protocol Table 1 seems to imply that trial participants will be follow-up for up to 2 years’ post-randomisation. What about the analysis and reporting of longer term outcomes?

The repeated outcome assessments, post-randomisation, need to be analysed by either creating a summary measure such as the mean score post randomisation or AUC; or using a longitudinal model.

Also it appears that control participants can “cross over” at the end of six months to receive the intervention. How will this longer term outcome data be analysed?

“At the end of the 6-month program, maintenance messages will be sent to intervention subjects for a further 6 months at a frequency of 2 per week. Control subjects will be offered the opportunity to receive the SupportMe intervention at that point.”

We are no longer planning to undertake statistical analyses of any data obtained after 6 months. Whilst this was the original intention, we do not have sufficient funding to undertake this, and this will logistically be very challenging. We now plan just to undertake voluntary surveys to obtain feedback about the acceptability of the program and health status. The purpose if this is largely to guide future program development. As this is not a core part of the trial we have decided not to expend our word count describing these details in the protocol paper. These details however will be included in the amended protocol for ethics. Offering the Control subjects the intervention is not to produce a crossover for analysis. Rather, it is to enable all participants to have the opportunity to experience the intervention.

The reporting of Serious Adverse events should be clearly described.

Table 1 Schedule of events in the protocol should be included in the protocol paper.

We have added in a section on serious adverse events: “We will record serious adverse events (SAEs) which are fatal, life-threatening, medically important, result in hospitalisation or prolongation of hospitalisation, or cause disability or incapacity. The Clinical Endpoint Adjudication Coordinator (CEAC) will determine whether the event will need adjudication. SAEs related to diabetes or cardiac disease will be adjudicated by an independent physician.”

The trial management arrangements e.g. TMG; TSC and DMEC appear to be satisfactory. Does the DMEC need an independent statistician?

We do not feel that a trial of this nature requires an independent statistician on the DMEC as there should be no risks and we are unlikely to terminate the study early on the basis of statistical reasons.