Mobile phone text messaging to improve adherence to cardiovascular disease secondary prevention interventions (Protocol)

Adler AJ, Martin N, Mariani J, Tajer CD, Serrano NC, Casas JP, Perel P

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[Intervention Protocol]

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine whether mobile phone text messaging is effective in enhancing adherence to recommended medication in patients with established arterial occlusive events.

BACKGROUND

Description of the condition

Worldwide, there are an estimated 13 million deaths due to coronary heart disease or stroke each year, and 80% of these deaths occur in low- and middle-income countries (Lozano 2012). It is estimated that approximately three times as many people will suffer non-fatal cardiovascular events and that each year 35 million people have an acute coronary or cerebrovascular event. Worldwide at least 100 million people are thought to have prevalent cardiovascular disease (Chambless 1997; WHO 2002; Yusuf 2011). This population has a five times greater chance of suffering a new cardiovascular event than people without known cardiovascular disease (Kerr 2009).

Secondary cardiovascular disease prevention is defined as action aimed to reduce the probability of recurrence of a cardiovascular event in patients with known atherosclerotic cardiovascular disease. There are two main aspects to secondary cardiovascular disease prevention: risk factor management and medications. Drug interventions (such as anti-platelet therapy, ACE inhibitors, beta-blockers and statins) have been shown to be cost-effective in reducing the risk of subsequent fatal and non-fatal cardiovascular events in patients with established atherosclerotic cardiovascular diseases and are recommended in international guidelines (ESC 2012; Smith 2011; WHO 2003).

Unfortunately there is a well-documented knowledge-practice gap in the implementation of these proven cost-effective interventions.

For example, the Prospective Urban Rural Epidemiology (PURE) study reported that in low- and middle-income countries up to 75% of patients with known cardiovascular disease are not using even one recommended medication (Yusuf 2011). Even in high-income countries adherence to recommended treatments remains sub-optimal. A cross-sectional survey of 12 European countries showed only 26% of patients on antihypertensives achieving control of hypertension and less than 31% of patients on lipid-lowering medication achieving cholesterol control (Kotseva 2010). It has been shown that a considerable proportion of cardiovascular events could be attributed to poor adherence, with 9% of cardiovascular events in Europe attributed to poor adherence. It is estimated that good adherence may be associated with a 20% lower risk of CVD and 35% reduction in all-cause mortality (Chowdhury 2013). This evidence-practice gap might be influenced by different factors, including health system issues such as lack of accessibility and affordability; treatment complexity; or patients' non-compliance with recommendations (Nieuwlaat 2013). In order to influence non-compliance there is a need to develop scalable and cost-effective behaviour-change interventions.

Description of the intervention

Globally the number of mobile phone subscribers is estimated at nearly 7 billion. Even in low- and middle-income countries the penetration rate of mobile phones is estimated to be 90% (ICT 2014). The widespread ownership of mobile phones and the possibility of automation leads to a potential to deliver behaviour-change interventions to large numbers of people at low cost. Mobile phone interventions are a potentially promising means to deliver messages to increase medication adherence.The use of mobile devices such as phones to support the delivery of medical care is commonly referred to as mHealth.

How the intervention might work

Mobile phone text messages have been shown to improve medication adherence for a variety of conditions including HIV (Sharma 2012). Two recent systematic reviews addressed the question of using mobile phones for all types of medication adherence (Anglada-Martinez 2015; Park 2014). The majority of studies found significant improvement in medication adherence through the use of text messages. Overall few adverse events have been reported with mobile phone text messaging; however, potential rare adverse effects such as road traffic accidents may occur.

Why it is important to do this review

While there is a great deal of enthusiasm for mobile health interventions among researchers and policy makers, there is still limited evidence for its effectiveness (Free 2013). Systematic reviews have been recently conducted on adherence to medications and reported promising results (Anglada-Martinez 2015; Park 2014); however, to date no systematic review has been conducted evaluating specifically the effect of mobile phone text messaging on secondary cardiovascular disease prevention. Mobile phone text messaging is of particular interest in low- and middle-income countries because of wider accessibility of mobile phones with text-messaging capabilities than smartphones.

OBJECTIVES

To determine whether mobile phone text messaging is effective in enhancing adherence to recommended medication in patients with established arterial occlusive events.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We will include all people with established arterial occlusive events, including coronary artery disease, cerebrovascular artery disease, peripheral artery disease, and atherosclerotic aortic disease, for whom antiplatelet, blood-pressure lowering medications and lipid-lowering medications are recommended. We will include all studies regardless of where the patients were enrolled (community or clinic). We will only include studies where at least 50% of participants have established CVD.

Types of interventions

We will include trials comparing interventions using short message service (SMS) or multimedia messaging service (MMS) to improve adherence to secondary cardiovascular prevention interventions. We will compare mobile phone messaging with no intervention, and also with other modes of communication (for example, face-to-face, postal letters, or phone calls). We will not exclude studies based on how the text messages were developed, or if they were one way versus two ways. We will only include trials that include adherence, but we will also include trials that include adherence and lifestyle modifications.

Types of outcome measures

Primary outcomes

1. Adherence to treatment (any definition used in trials)
2. Fatal cardiovascular events
3. Non-fatal cardiovascular events (CHD, revascularisation, stroke)
4. Combined CVD event (fatal or non-fatal events)

Secondary outcomes

1. Surrogate outcomes according to the different interventions recommended for secondary prevention including:
   - LDL-cholesterol for the effect of statins,
   - blood pressure for antihypertensive drugs,
   - heart rate for the effect of atenolol,
   - urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin.

2. Adverse effects including self reported road traffic accidents and repetitive thumb strain.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*
- MEDLINE (Ovid)
- EMBASE (Ovid)
- Conference Proceedings Citation Index-Science (CPCI-S) on Web of Science (Thomson Reuters)

The preliminary search strategy for MEDLINE (Ovid) (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximising RCT filter will be applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL (Lefebvre 2011).

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov); and the World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all included primary studies and review relevant articles for additional references.

Data collection and analysis

Selection of studies

Two of three review authors (AJA, NM, NS) will independently screen titles and abstracts for inclusion of all identified potential studies and decide to retrieve the full-text copies or to discard them. If there are any disagreements, a third author will arbitrate (PP or JPC). We will retrieve full-text study reports/publications and two of three review authors (AJA, NM, NS) will independently screen the full text and identify studies for inclusion. We will resolve any disagreement through discussion. If necessary, a third person (PP or JPC) will arbitrate. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, instead of the report, is the unit of interest in the review. We will complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form to extract study characteristics and outcome data previously piloted on at least one study in the review. Two review author (NM and AJA) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range, gender, condition, diagnostic criteria, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, excluded medications, how text messages developed, behaviour change technique, time from arterial occlusive event, if SMS was personalised.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

We will resolve disagreements by consensus or by involving a third person (PP or JPC). One review author (AJA) will transfer data into the Review Manager 5 (RevMan 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two of three review authors (CT, JM, AJA) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion. If necessary another author (JPC) will arbitrate. We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other biases including industry funding

We will grade each potential source of bias as high, low or unclear and provide evidence from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios or risk ratios with 95% confidence intervals and continuous data as mean difference or standardised mean difference with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

Parallel design and cluster randomised trials will be included. If we find cluster randomised trials then we will ensure that we use appropriate analysis accounting for the cluster design. If the authors do not report the appropriate analysis, we will calculate correct estimates using the intracluster correlation coefficient.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (greater than 50%), then we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials then we will create and examine a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We will undertake meta-analyses only where this is meaningful (i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense).

Because we foresee heterogeneity between studies we will use a random-effects model.

Summary of findings table

We will create a 'Summary of findings' table using the following outcome: adherence to treatment. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software. We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

If there are sufficient studies and information, we plan to carry out the following subgroup analyses for the primary outcome.

1. The baseline ASCV condition (i.e. coronary artery disease, cerebrovascular artery disease, peripheral artery disease, and atherosclerotic aortic disease)
2. Age (non-elderly versus elderly, i.e. 64 or more years old)
3. According to the health system in the population background (universal health systems versus others)
4. Income region (by World Bank income group)
5. Type of setting (private versus public, and rural versus urban)
6. Time of duration of the intervention (less than 1 year versus 1 year or more)
7. Time since cardiovascular event (less than 1 year versus 1 year to 2 years versus 2 years or more)

8. Frequency of text messages (daily versus other)
9. How text messages are developed (theory-based, validated, etc.)
10. If trials are text message only or text message plus phone calls
11. By different measurements of adherence reported in the articles (for example MARS questionnaire, self-reported, pill recounts, etc.)

Sensitivity analysis

We plan to carry out the following sensitivity analysis.
1. Only including studies with a low risk of bias

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline the remaining uncertainties.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary search strategy - MEDLINE (OVID)

1. Reminder Systems/
2. Telemedicine/
3. exp Cell Phones/
4. sms.tw.
5. mms.tw.
6. (short adj messag*).tw.
7. (text adj messag*).tw.
8. texting.tw.
9. telemedicine*.tw.
10. (reminder adj (text* or system* or messag*)).tw.
11. telehealth.tw.
12. (mobile adj (health* or phone*)).tw.
13. mhealth.tw.
14. telemonitor*.tw.
15. or/1-13
16. exp Cardiovascular Diseases/
17. cardio*.tw.
18. cardia*.tw.
19. heart*.tw.
20. coronary*.tw.
21. angina*.tw.
22. ventric*.tw.
23. myocard*.tw.
24. pericard*.tw.

25. isch?em*.tw.
26. emboli*.tw.
27. arrhythmi*.tw.
28. thrombo*.tw.
29. atrial fibrillat*.tw.
30. tachycardi*.tw.
31. endocardi*.tw.
32. (sick adj sinus).tw.
33. exp Stroke/
34. (stroke or strokes).tw.
35. cerebrovasc*.tw.
36. cerebral vascular.tw.
37. apoplexy.tw.
38. (brain adj2 accident*).tw.
39. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
40. peripheral arter* disease*.tw.
41. aortic*.tw.
42. (arterial adj occlus*).tw.
43. infarct*.tw.
44. or/16-43
45. 15 and 44
46. randomized controlled trial.pt.
47. controlled clinical trial.pt.
48. randomized.ab.
49. placebo.ab.
50. drug therapy.fs.
51. randomly.ab.
52. trial.ab.
53. groups.ab.
54. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. exp animals/ not humans.sh.
56. 54 not 55
57. 45 and 56

CONTRIBUTIONS OF AUTHORS

AJA: writing of review, screening, analysis

NM: screening, extracting, search strategy

JM: risk of bias tables

CT: risk of bias tables

NS: screening, extraction and consulting on design and methods

JPC: arbitration of disagreement, consulting on design and methods

PP: proposal, writing, arbitration of disagreement, consulting on design and methods

DECLARATIONS OF INTEREST

AJA: nothing to declare

NM: nothing to declare

JM: nothing to declare

CT: has collaborated with Bristol Myers Squibb and Pfizer to provide expert testimony and lectures. These have been unrelated to the subject matter of this review.

NS: nothing to declare

JPC: nothing to declare

PP: nothing to declare

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