BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033017
Article Type:	Protocol
Date Submitted by the Author:	16-Jul-2019
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Keywords:	Mobile health, Discontinuation rate, Dual antiplatelet therapy

Rationale and Design of the Web basEd soCial media tecHnology to improvment in Adherence to dual anTiplatelet Therapy following Drug-Eluting Stent Implantation(WECHAT): protocol for a randomized controlled study

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Conflicts of Interest: None.

Ethics and dissemination: Ethical approval has been obtained from Guangdong General Hospital.

Trial registration: ClinicalTrials.gov. NCT03732066

Strengths and limitations of this study:

This multicentre trial will firstly and comprehensively provide the evidence for effectiveness of mobile health (mHealth) technology on health management and drug compliance of four kinds of cardioprotective medications.

Internet-based counseling is a new approach to motivate patients' stickiness and obtain patients' feedback . There are not many studies that focus on the internet-based counsult through systematic review.

At present, the performance of mobile health (mHealth) techonology still remain unclear in patients aged 65 years and older who may not even use a smartphone. The age distribution of the patients enrolled in the study may not be able to contain too many elderly people >65 years old.

The causes of discontinuation of either drugs, such as drug charges, gastrointestinal reactions and allergies to aspirin, couldn't be collected and classified.

Abstract

Background: Dual antiplatelet therapy (DAPT) is frequently discontinued after drug-eluting stent (DES) implantation, which could increase risk of major adverse cardiovascular events (MACEs). Few studies have attempted to improve DAPT adherence through web based social media.

Objective: To explore the effect of social media on DAPT adherence following DES implantation.

Methods/Design: The WECHAT trial, a multicenter, double-blind, randomized study (1:1), will recruit 760 patients requring 12 months DAPT after DES implantation. The intervention group will receive personalized social media intervention (interactive responses, medication reminders, medical knowledge education and follow-up reminders) four times a week; conversely, the control group will receive average social media message (medical knowledge education and follow-up reminders). The primary endpoint will be the discontinuation rate of any antiplatelet drug within 1 year after DES implantation. The secondary endpoints will include medication adherence evaluated by proportion of days covered (PDC) and major adverse cardiovascular events(MACE), including all-cause mortality,target vessel revascularization, non-fatal myocardial infarction, and stroke.

Conclusion: This study will firstly evaluate the efficacy of social media in improving compliance to DAPT, which is expected to explore novel strategies to improve drug compliance.

Keywords: Mobile health; Discontinuation rate; Dual antiplatelet therapy; Drug-eluting stent implantation; Cross-sectional survey; Randomized controlled trial

Introduction

With the aging population and increasing prevalence of cardiovascular risk factors, the disease load of coronary heart disease (CHD) will increase dramatically in the futur[1,2]. According to the recent European guidelines on myocardial revascularization, 12 months dual antiplatelet therapy (DAPT) is generally recommended in patients drug-eluting stent (DES) implantation[3]. Despite the conclusive evidence on the effectiveness of DAPT demonstrated in previous studies[4,5], approximately 9.8% of patients discontinued antiplatelet therapy by themselves during the 1-year follow-up period, the overall discontinuation rate was as high as 23.3%[6]. DAPT discontinuation could lead to higher major adverse cardiovascular event (MACE) risks[7], while medication adherence improvement could reduce such risks[8,9].

With the development of communication tools, social media has become an important communication platform to prevent cardiovascular diseases[10,11], and interventions based on such have gradually become a low-cost means to improve the health of patients with chronic diseases, including CHD. Some previous studies in different countries[12,13] have proven that many different type of interventions , such as patients' education, counselling, drug reminders, can improve patients' medication adherence as well as control short-term risk factors. The supporter for these categories included emails, messages, website, facebook and so on[13]. However, few studies have focused on improving DAPT adherence of patients following drug-eluting stent (DES)

implantation via social media,especially via wechat. In addition, the counselling in thoese studies were provided only limited times. Therefore, we designed this multicenter, double-blind, randomized study to explore the prevalence of DAPT discontinuation and the effect of using social media on DAPT adherence among patients needing 1 year DAPT therapy following DES implantation.

Methods

Study Design

WECHAT study is a multicenter, double-blind, randomized controlled trial that will be conducted in the Department of Cardiology of five hospitals. A total of 760 patients in 4 hospitals in Guangdong province who undergo DES implantation will be enrolled; Guangdong General Hospital institutional ethics review board has approved the study's design（Figure 1）. Participants will be randomly allocated to either the control group or intervention group. The control group will be assigned to receive messages four times a week only, while the intervention group will be allocated to receive interactive responses medication reminders, medical knowledge education and follow-up reminders, in addition to messages.

Data collection

Patients in both the intervention group and control group will be required to provide baseline information, including social demographic characteristics, history of disease, and social behavior characteristics, such as smoking status and sports activity. They will also be required to enter the applet as soon as they are enrolled. They will undergo 4th-, 8th-, and 12th-month visits during the 12 months of follow-up.

Study Population

Patients aged ≥18 years undergoing DES implantation within 7 days will be eligible for the study. Meanwhile, they should take DPAT at least 1 year after doctor's evaluation. Written informed consent should be provided. Patients will be excluded for the following reasons: pregnancy; malignant tumor or end-stage disease with a life expectancy of <1 year; refusal to use social media; and refusal to provide written informed consent for this study. Our enrollment and randomization haven't started yet. But we have enrolled 36 patients undergoing DES implantation for internal testing. All patients were assigned to intervention group and have received personalized social media intervention four times a week.

Randomization and Blinding

Randomization will be performed using a centralized, computerized randomization program in a uniform 1:1 allocation ratio. The intervention program will be initiated after the patients are enrolled; the patients (but not their care providers), research personnel, and investigators will be unaware of their allocation. Study coordinators and research assistants conducting the assessments and statisticians will also be blinded. This randomization program is electronically linked to the applet that will deliver the interactive response and message, thereby minimizing the need for human interference. Key participant characteristics that will determine intervention customization and personalization will also be automatically imported into the applet administering the intervention.

Study Intervention

A total of 760 qualified patients will be randomized using computer-generated random numbers at a 1:1 ratio to be classified into either the intervention group (interactive responses, medication reminders, medical knowledge education and follow-up reminders) four times a week) or control group (medical knowledge education and follow-up reminders). This randomization program is electronically linked to the applet that will deliver the intervention, thereby minimizing the need for human interference.

Control Group

The preliminary content settings will include health education, long-term drug withdrawal warning interface, lifestyle intervention, medication reminder, doctor advice, follow-up reminder, and clock in mode.

The control group will receive standard care as determined by their usual doctors. Typical secondary prevention cardiovascular medications include antithrombotic drugs, β-blockers, statins, and angiotensin converting enzyme inhibitor (ACEIs)/angiotensin II receptor blockers(ARBs). These patients will also receive usual messages four times a week, including cardiovascular knowledge and follow-up reminders, such as risk factors for CHD and typical symptoms of myocardial infarction. The patients will be followed up on the 4th, 8th, and 12th months and undergo physical examination, lifestyle assessment, drug adherence status evaluation, and therapy adjustment.

Intervention Group

The intervention group will receive usual messages (as described above), with additional personalized reminders that will include a series of messages focusing on medication adherence. Meanwhile, they will also be provided with contact to auto-responses and backstage counsel over the 12-month study period as detailed below.

The interventions for this group are listed but not limited to the following points:

1) Medication Reminders

1. Patients' personal information will be assessed when they are enrolled. The mHealth tools will provide special interventions according to the patients' medical history. For example, patients with hypertension will receive daily reminders on blood pressure measurement and medication. They will also receive early warning on hypertension with a systolic blood pressure of >180 mmHg or <90 mmHg. Patients who smoke will be required to quit smoking. Every patient will receive a Health Report monthly, which will reflect their drug compliance, blood pressure, heart rate, low-density lipoprotein cholesterol level, and smoking status.

2. Patients' medication information will be recorded by obtaining pictures of their medication. Patients will be asked to punch time clocks simply in the mHealth tools. If they forget to punch cards, they can punch cards whenever they think of it. If there is no record of medication for 3 days, SMS alerts will be received, and phone calls will be received over 7 days.

2) Interactive Responses

1. Auto-Response: After sending personal or discomfort symptom questions, the

patients will be provided with an automatic response pushed by the back-end database by crawling the keywords. It is suggested that the answer is just for reference. In case of urgent questions, they will be advised to consult the clinicians.

2. The researchers will communicate with the patients once a month.

Follow-Up

Blood pressure, heart rate, heart rhythm, body weight, lifestyle assessment findings, medication, and medication adjustment will be recorded at 4th, 8th and 12th months after enrollment. The medication adherence of the patients will be evaluated by PDC covered. MACEs will include all-cause mortality, rehospitalization, target vessel revascularization, and stroke. All information will be carefully collected by the research staff through outpatient/telephone follow-ups.

Timeline：

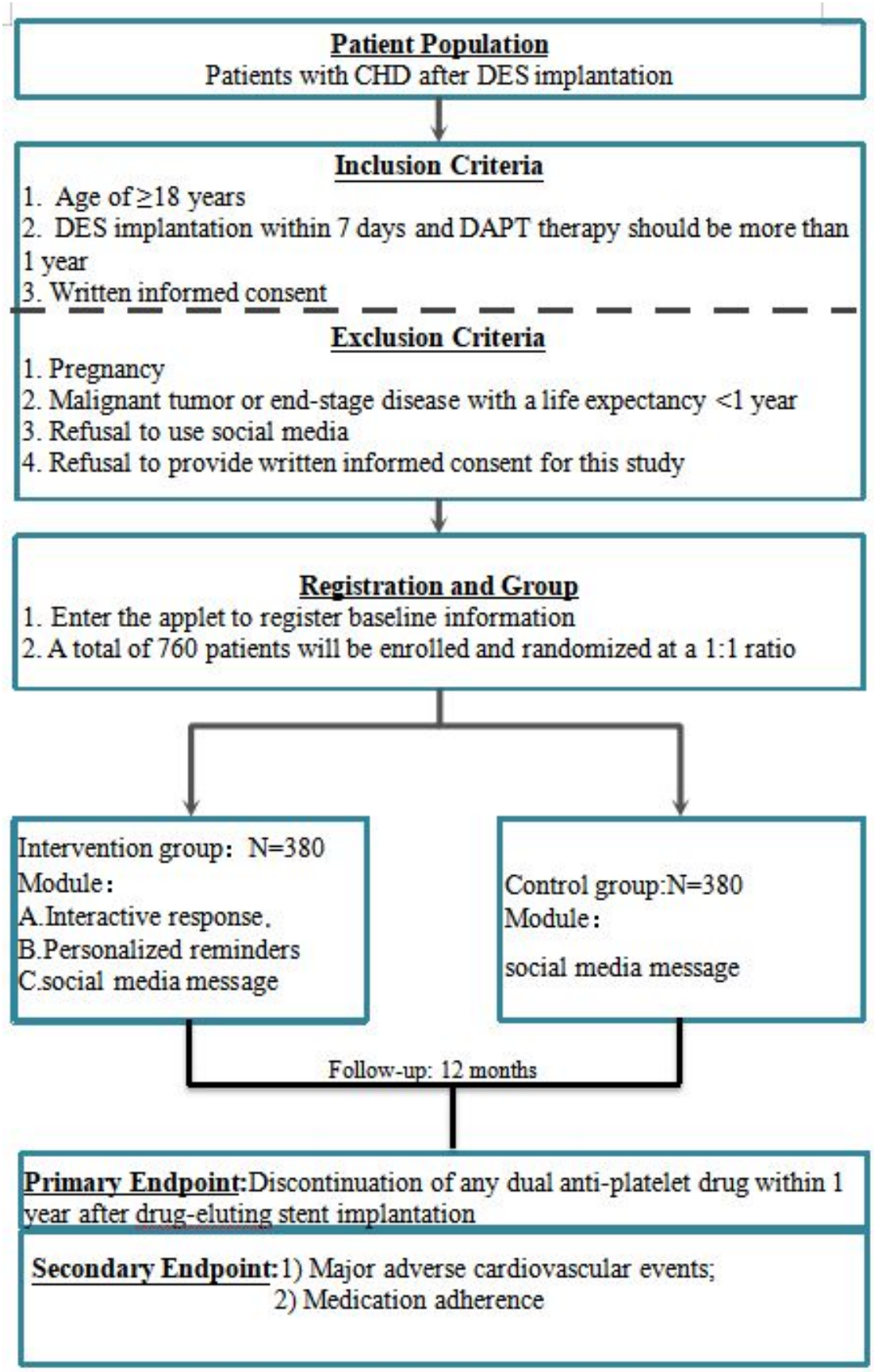
2018/06/01-2018/09/31 Ethical application for research proposal should be approved by tthe Institutional Review Board of Guangdong General Hospital Ethics Research Committee

2018/10/01-2018/12/31 Mobile health tools are developed via cooperating with relevant technology companies and some patients will be enrolled for internal testing.

2019/01/01-2020/12/31 Enrollment will be completed during the 4 months and at least 760 patients will be randomly allocated to either the control group or intervention group.

2021/12/01-2022/01/01 Follow-up and interim analysis are expected to be accomplished.

Figure 1. Flow chart of study design



CHD: coronary heart disease

DAPT:Dual Antiplatelet Drug

DES:Drug-eluting stent

Study Endpoints

1) Primary Outcome

The primary endpoint will be the discontinuation of any antiplatelet drug within 1 year after DES implantation. The discontinuation duration will be further segmented into periods after the index disruption event, i.e, brief (1–7 days), temporary (8–30 days), and permanent (>30 days) according to follow-up and records of medication adherence in social media.

2) Key Secondary Outcomes

The secondary endpoints will be as follows:

1. Medication Adherence: We will assess the patients' DAPT adherence according to PDC recorded by prescription.

2. MACEs, including all-cause mortality,target vessel revascularization, non-fatal myocardial infarction, and stroke.

Definition

DAPT is defined as the combination of aspirin and an oral inhibitor of the P2Y12 receptor for adenosine 5'-diphosphate[14].

Oral inhibitors of the P2Y12 receptor include ticagrelor and clopidogrel[15]. Other drugs, such as prasugrel, will not be included because they are not yet available in the Chinese market.

Medication change will be defined as the change between ticagrelor and clopidogrel under doctors' advice(Table 1).

Table.1 Outcome Definitions

Term	Definition
Dual antiplatelet drug discontinuation	Defined as discontinuation of any dual antiplatelet drug owing to patients' own discretion, including bleeding or non-compliance rather than doctors' advice. Changing of DAPT medication between ticagrelor and clopidogrel under doctors' advice will not be identified as dual antiplatelet drug discontinuation; changing of such under own discretion will be identified as such[6].
Dual antiplatelet drug disruption	Defined as temporary discontinuation of antiplatelet treatment owing to surgical necessity with reinstitution of DAPT within 14 days[6]
Dual antiplatelet drug discontinuation duration	Duration of discontinuation is further divided into brief (1–7 days), temporary (8–30 days), and permanent (>30 days)[6].
Medication adherence	Medication adherence is further divided into poor (PDC<40%), moderate (40-80%), and good (PDC>80%) according to the prescription
All-cause mortality	Defined as any death recorded between the date of enrollment and the end of data linkage[16]
Target vascular revascularization	Defined as any revascularization procedure (PCI or CABG) involving the vessel treated during the index PCI procedure
Non-fatal myocardial infarction	Typical rise and fall of biochemical markers of myocardial necrosis to greater than twice the ULN or if markers were already elevated, further elevation of a marker to >50% of a previous

	value that was decreasing and >2 × ULN, with ≥1 of the following: 1) ischemic symptoms, 2) development of new pathologic Q waves, 3) ECG changes of new ischemia, or 4) pathologic evidence of MI[3].
Stroke	Any stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting >24 h. It is strongly recommended (but not required) that an imaging procedure, such as computed tomography or magnetic reso1nance imaging, be performed.
Major adverse cardiovascular events	the composite of all-cause mortality,target vessel revascularization, non-fatal myocardial infarction, and stroke

Reporting and Evaluation of Clinical Adverse Events

The researchers in each center will carefully observe the main clinical adverse events that will occur during the clinical study, inquire and check them carefully according to the "Clinical Incident Registration Form," fill out the "Clinical Event Registration Form" in Case Report Form， and save relevant clinical data. Clinical data related to clinical adverse events should be reported to the Department of Cardiology, Guangdong General Hospital, Guangdong Institute of Cardiovascular Diseases and the sub-center's clinical event committee for assessment of the clinical events reported by each clinical center. At least two specialist clinicians will be

required for confirmation. Any symptoms of discomfort will be self-reported via social media.

Data and Safety Monitoring Board

A committee of clinicians and a biostatistician will periodically review and evaluate the accumulated study data for participants' safety, progress (if appropriate), and efficacy, making recommendations to the principal investigators concerning the continuation, modification of enrollment, or termination of the trial. The academic committee of our hospital has approved the study' s design.

Ethics and Dissemination

This study will follow the principles of the Good Clinical Practice(GCP) and the Helsinki Declaration. Before the initiation of the trial, the PI of the sub-center will be responsible for submitting the necessary information, such as research plan, and informed consent to their ethics committee for review. It will be the responsibility of the investigator to explain the purpose, methodology, benefits, and potential adverse events of the interventions of the study. All patients enrolled will be required to provide written informed consent for this study. For patients who are unable to make a legally binding decision for any reason, the investigator must obtain the informed consent from their legal parent or their legal guardian.

Statistical Analysis

The sample size calculation will be based on a previous study[6]. With a test level of 0.05, test efficiency of 80%, 1-year incidence rate in the control group of 24%, 1-year

incidence rate in the test group of 15%, significance level of 0.05, power of 90%, and dropout rate of <20% obtained using nQuery + nTerim 3.0 (Statistical Solutions Ltd., Farmer's Cross, Cork, Ireland) with a two-sided chi-square test, 380 subjects will be required in each group, and a total of 760 patients will be needed in the two groups.

Comparisons between normally distributed continuous variables, expressed as means ± standard deviations, will be performed using two-sample t-tests; non-normally distributed continuous variables, presented as medians and interquartile ranges, will be analyzed using Wilcoxon rank-sum tests. Pearson chi-square or Fisher' exact tests will be used, as appropriate, for categorical data, which will be expressed as percentages. The primary and secondary endpoints will be analyzed in accordance with the intention-to-treat principle. All tests will be two-tailed, and a p value of <0.05 will be considered statistically significant. To account for group effects and correct baseline characteristics, the primary endpoint will be compared using a generalized assessment equation, and the SAS version 9.3 will be employed for all analyses.

Table 2 Characteristics of randomized controlled trials with intervention to improve patients' lifestyle among patients with coronary heart disease

Study	Design	Duration	Population	Primary endpoint & Secondary endpoint	Experimental group vs Control group
Karla et al 2018[17]	RCT	3months	163 patients with CHD	Drug adherence (MMAS-8 score) &Blood pressure and cholesterol levels	**Intervention group** Basic APP:alarm Advanced APP:record and snooze the pause **Control group** -usual medical care
Salvi et al, 2018[18]	RCT	24 months	118 patients with MI	Education level about heart-related health improve more in the intervention groups(p=0.01). Exercise habits improved without statistical significance.	**Intervention group** -the mobile station: a wearable sensor capable with app -the patient station: feedback and educational information -the professional station: monitor patients and generates alerts

					Control group -receiving standard rehabilitation
Bravo-Escobar et al, 2018[19]	RCT	2 months	28 patients with stable CHD at Moderate cardiovascular risk	Exercise time. & quality of life score	**Intervention group** -hospital exercise once a week -exercised at home following a program monitored with a remote electrocardiographic device **Control group** -hospital exercise 3 times a week -encourage to do exercise at home
Clara et al, 2016 [12]	RCT	6months	710 patients with CHD	LDLC &Systolic blood pressure, body mass index (BMI), physical activity, and smoking status.	**Intervention group** -TM providing lifestyle advice ,motivational reminders, and support to change lifestyle behaviors.(four times a week) -usual medical care **Control group**

					-usual medical care
Linda et al, 2015[20]	RCT	30 days	90 patients with CHD	There was no significant difference in the improvement as a function of the different treatment groups (F (2,6.24) =0.45, p=0.64).	**TM Reminders+ TM Education group** -two-way reminders messages on drug -one-way health messages **TM Education group** -one-way health messages **Control group** -Usual care/No TM
Leila et al, 2015[21]	RCT	6 months	123 patients with CHD	The intervention group reported significantly greater medication adherence score (mean difference: 0.58, 95% CI 0.19-0.97; P=.004).	**Intervention group** -24 week text message program and access to website -Standard CR services -3-month phone call **Control group** -Standard CR services -3-month phone call

Vernooij et al, 2012[22]	RCT	12 months	330 patients with atherosclerosis.	A relative change of -12% (-22% to -3%) in Framingham heart risk score for the intervention group compared with the usual care group	**Intervention group** -Personalized website -Nurse reminder **Usual care group** -Usual care by doctor
Blasco et al, 2012[23]	RCT	12 months	203 patients with ACS	Telemonitoring group experience improvement in cardiovascular risk factors profile than control patients (RR 1.4;95% CI 1.1-1.7)	**Telemonitoring group** -health data website -health recommendation messages -lifestyle counseling -usual-care treatment **Control group** -lifestyle counseling -usual-care treatment
Robert et al, 2012[24]	RCT	6 months	223 patients after PCI without	Emotional ($p<0.038$) and physical ($p< 0.031$) dimensions of heart disease	**Intervention group** -6-month online tutorials -feedback email

	enrolling in cardiac rehabilitation.	health-related quality of life were higher in CardioFit group.	**Control group** -physical activity guidance from doctors and book

RCT=randomized controlled trial

TM=text messages

CR=cardiac rehabilitation

Discussion

We hypothesize that the interventions through social media would yield a better DAPT adherence in patients with CHD who underwent DES implantation within 1 year.

Despite the conclusive evidence on the effectiveness of DAPT, DAPT discontinuation occurs frequently owing to various reasons, which could lead to many adverse outcomes. Mehran et al[6] enrolled 5018 patients who underwent percutaneous coronary intervention and found that approximately 14.4% of patients discontinued antiplatelet therapy by themselves owing to bleeding or poor adherence during the 2-year follow-up period. The incidence of MACE, stent thrombosis, and re-infarction increased significantly in the drug discontinuation group compared with that in the drug continuation group. Improving medication adherence has shown important effects on the long-term prognosis of patients with CHD[25,26]

Previous studies have shown that using mobile medical interventions, which are even simple methods, can improve patients' lifestyle and risk factors(Table 2). The SimCard Trial[19] has shown that management with the use of social media can improve the blood pressure control rate in Asians[13,27]. It provided evidence that smartphones can promote multifactorial interventions for secondary prevention of CHD. The TEXT ME study[12], a randomized controlled trial with 6 months of follow-up, enrolled 710 patients with CHD. The intervention group received four messages per week, which included four aspects: smoking intervention, diet, physical activity, and general coronary health education. Conversely, the control group

received standard care only. The low-density lipoprotein cholesterol level, systolic blood pressure, and body mass index significantly improved in the intervention group. Although the TEXT ME study was a single-center study with only 6 months of follow-up, it provided a good model for other mobile-based intervention research and design through social media.

Although the concept of social media-based interventions is not new, it may be a good method to promote medication adherence considering the rapidly increasing application ratio of smartphones[28-30]. Through the analysis of our previous questionnaire, as well as investigation of the current chronic disease management software in the market, the clinical team and academic team of our project and the technology company jointly developed the CHD management program, which has been internally verified and externally qualified. Rather than creating a brand-new application, our applet is based on WECHAT, which has approximately 700 million active users. Our applet will intervene the patients and their families in various aspects, e.g., lifestyle, health education, self-management, supervision, behavioral and medical consultation, and treatment adherence evaluation, which are associated with improvement of communication efficiency and patients' compliance.

In conclusion, we designed this double-blind, multicenter, randomized study to explore whether a social media-based intervention will be effective in enhancing DAPT compliance across multiple hospitals among patients with CHD who underwent DES implantation within 1 year.

Limitations

There are some potential limitations in our research. Most patients with CHD are old, and the exact proportion of 65-year-old individuals using smartphones is not known. However, for those who are unable to use social media, we may intervene their families to ensure that our targets are provided with individualized interventions. We also designed an appropriate intensive reminder system and incentive system, e.g., telephone notification for long-term non-check-in. Regardless of the abovementioned limitation, the findings of this trial will have important implications for clinical practice.

Highlights

- Dual antiplatelet therapy (DAPT) is the basic treatment for patients who underwent drug-eluting stent implantation within 1 year.
- For various reasons, DAPT discontinuation is common and could lead to many adverse outcomes.
- Interventions through social media may be an effective and easy method to strengthen medication adherence.
- This study examined an intervention (medication adherence information reminder, personalized lifestyle advice, online interaction, and self-report system) through the WECHAT applet for these patients.
- DAPT discontinuation and medication adherence and major adverse cardiovascular events were the primary and secondary endpoints, respectively.

Contributors: All authours are responsible for the design and conduct of this study. Guoli Sun, Li Lei, Liwei Liu wrote the first draft of the protocol manuscript. Yong

Liu, Ji-yan Chen drafted the work and revised it critically for important intellectual content.

Funding : The study was supported by grants from the Guangdong General Hospital Clinical Research Fund (2014dzx02.) , Cardiovascular Research Foundation Project of the Chinese Medical Doctor Association (SCRFCMDA201216) and Science and Technology Planning Project of Guangdong Province (2014B070706010) as major funding bodies.

Competing interests : None declared.

Ethics approval: This study was conducted with the approval of the Institutional Review Board of Guangdong General Hospital Ethics Research Committee and all other participating sites.

Provenance and peer review: Not commissioned; externally peer reviewed.

REFERENCE

1. Lin JS, Evans CV, Johnson E,*et al*. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2018;32:281-97.

2. Writing Group M, Mozaffarian D, Benjamin EJ, *et al*. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133:e38-360.

3. Neumann FJ, Sousa-Uva M, Ahlsson A, *et al*. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

4. Ferrieres J, Lautsch D, Ambegaonkar BM, et al. Use of guideline-recommended management in established coronary heart disease in the observational DYSIS II study. *Int J Cardiol*. 2018;270:21-7.

5. Kedhi E, Fabris E, van der Ent M, *et al*. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ.* 2018;363:k3793.

6. Mehran R, Baber U, Steg PG, *et al*. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *The Lancet*. 2013;382:1714-22.

7. Cutlip DE, Kereiakes DJ, Mauri L, *et al*. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv.* 2015;8:404-10.

8. Irvin MR, Shimbo D, Mann DM, *et al*. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich)*. 2012;14:694-700.

9. Durand H, Hayes P, Morrissey EC, *et al*. Medication adherence among patients

with apparent treatment-resistant hypertension: systematic review and meta-analysis. *J Hypertens*. 2017;35:2346-57.

10. Patel R, Chang T, Greysen SR, *et al*. Social Media Use in Chronic Disease: A Systematic Review and Novel Taxonomy. *Am J Med.* 2015;128:1335-50.

11. Redfern J, Ingles J, Neubeck L, *et al*. Tweeting our way to cardiovascular health. *J Am Coll Cardiol*. 2013;61:1657-8.

12. Chow CK, Redfern J, Hillis GS,*et al.* Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. *JAMA.* 2015;314:1255-63.

13. Widmer RJ, Allison TG, Lerman LO,*et al*. Digital Health Intervention as an Adjunct to Cardiac Rehabilitation Reduces Cardiovascular Risk Factors and Rehospitalizations. *J Cardiovasc Transl Res*. 2015;8:283-92.

14. Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213-60.

15. Hahn J-Y, Song YB, Oh J-H, Cho D-K, Lee JB, Doh J-H, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. The Lancet. 2018;391(10127):1274-84.

16. Liu Y, Chen JY, Huo Y, *et al.* Aggressive hydraTion in patients with

ST-Elevation Myocardial infarction undergoing Primary percutaneous coronary intervention to prevenT contrast-induced nephropathy (ATTEMPT): Study design and protocol for the randomized, controlled trial, the ATTEMPT, RESCIND 1 (First study for REduction of contraSt-induCed nephropathy followINg carDiac catheterization) trial. *Am Heart J*. 2016;172:88-95.

17. Santo Karla,Singleton Anna,Rogers Kris, *et al*. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial.*Heart.* 2018.10.1136/heartjnl-2018-313479

18. Salvi D, Ottaviano M, Muuraiskangas S, Martinez-Romero A, Vera-Munoz C, Triantafyllidis A, et al. An m-Health system for education and motivation in cardiac rehabilitation: the experience of HeartCycle guided exercise. J Telemed Telecare. 2018;24(4):303-16.

19. Bravo-Escobar R, Gonzalez-Represas A, Gomez-Gonzalez AM, *et al*. Effectiveness and safety of a home-based cardiac rehabilitation programme of mixed surveillance in patients with ischemic heart disease at moderate cardiovascular risk: A randomised, controlled clinical trial. *BMC Cardiovasc Disord*. 2017;17(1):66.

20. Park LG, Howie-Esquivel J, Whooley MA, *et al*. Psychosocial factors and medication adherence among patients with coronary heart disease: A text messaging intervention. *Eur J Cardiovasc Nurs*. 2015;14:264-73.

21. Pfaeffli Dale L, Whittaker R, Jiang Y, *et al*. Text Message and Internet Support for Coronary Heart Disease Self-Management: Results From the Text4Heart Randomized Controlled Trial. *J Med Internet Res*. 2015;17:e237.

22. Vernooij JW, Kaasjager HA, van der Graaf Y, *et al*. Internet based vascular risk factor management for patients with clinically manifest vascular disease: randomised controlled trial. *BMJ.* 2012;344:e3750.

23. Blasco A, Carmona M, Fernandez-Lozano I, *et al*. Evaluation of a telemedicine service for the secondary prevention of coronary artery disease. *J Cardiopulm Rehabil Prev.* 2012;32:25-31.

24. Reid RD, Morrin LI, Beaton LJ, *et al*. Randomized trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. *Eur J Prev Cardiol*. 2012;19:1357-64.

25. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. *The Lancet.* 2017;389:1055-65.

26. Vinogradova Y, Coupland C, Brindle P, *et al*. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. *BMJ.* 2016;353:i3305.

27. Tian M, Ajay VS, Dunzhu D, *et al*. A Cluster-Randomized, Controlled Trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk (SimCard Trial) in Rural Tibet, China, and Haryana, India. *Circulation.* 2015;132:815-24.

28. Santo K, Hyun K, de Keizer L, *et al*. The effects of a lifestyle-focused text-messaging intervention on adherence to dietary guideline recommendations in patients with coronary heart disease: an analysis of the TEXT ME study. *Int J Behav Nutr Phys Act*. 2018;15:45.

29. Dorje T, Zhao G, Scheer A, *et al*. SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol. *BMJ Open*. 2018;8:e021908.

30. Neubeck L, Lowres N, Benjamin EJ, *et al*. The mobile revolution--using smartphone apps to prevent cardiovascular disease. *Nat Rev Cardiol.* 2015;12:350-60.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title（P1）	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P1)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P5)	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale(P4)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses
Trial design(P4)	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting (P5)	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria (P6)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions (P7)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes(P12)	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline(P12)	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size(P15)	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment(P15)	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation(P7)	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)(P6)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods(P5)	18a	Plans for assessment and collection of outcome, baseline, 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
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management (P13)	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods(P13)	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval (P24)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent (P14)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests (P24)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy (P14)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Rationale and design of the Web basEd soCial media tecHnology to improvement in Adherence to dual anTiplatelet Therapy following Drug-Eluting Stent Implantation(WECHAT): protocol for a randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033017.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Oct-2019
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical management
Keywords:	Mobile health, Discontinuation rate, Dual antiplatelet therapy

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Rationale and design of the Web basEd soCial media tecHnology to improvement in Adherence to dual anTiplatelet Therapy following Drug-Eluting Stent Implantation(WECHAT): protocol for a randomised controlled study

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Conflicts of Interest: None.

Ethics and dissemination: Ethical approval has been obtained from Guangdong Provincial People's Hospital.

Trial registration: ClinicalTrials.gov. NCT03732066

Abstract

Background: Dual antiplatelet therapy (DAPT) is frequently discontinued after drug-eluting stent (DES) implantation, which could increase the risk of major adverse cardiovascular events (MACEs). Few studies have attempted to improve DAPT adherence through web-based social media.

Objective: To explore the effect of social media on DAPT adherence following DES implantation.

Methods/Design: The WeChat trial is a multicentre, double-blind, randomised study (1:1). It will recruit 760 patients with DES who require 12 months of DAPT. The control group will only receive usual care and general educational messages on medical knowledge. The intervention group will receive a personalised intervention, including interactive responses and medication and follow-up reminders beyond the general educational messages. The primary endpoint will be the discontinuation rate with 80% power, using a $\chi 2$ test. Discontinuation will be defined as the cessation of any dual antiplatelet drug owing to the participating patients' discretion within one year of DES implantation. The secondary endpoints will include medication adherence and major adverse cardiovascular events (MACE). Both groups will receive messages or reminders four times a week with follow-ups over 12 months.

Conclusion: The study will evaluate the effects of interactive responses and medication reminders via social media on improving DAPT compliance.

Keywords: Mobile health, Drug-Eluting Stents, Dual Antiplatelet Therapy, Randomised Controlled Trial

Strengths and limitations of this study:

This multicentre trial will provide comprehensive evidence of the effectiveness of mobile health (mHealth) on drug compliance with dual antiplatelet therapy and health management.

Internet-based counselling offers a new approach for motivating patient stickiness and obtaining patient feedback. There are few systematic reviews of interactive consultations.

At present, the performance of mobile health (mHealth) technology remains unclear in patients aged 65 years and older, because they may not use a smartphone. The age distribution of the patients enrolled in the study may not contain many people >65 years old.

The causes of discontinuation of either drug, such as drug changes, gastrointestinal reactions and allergies to aspirin, could not be collected and classified.

Introduction

With an aging population and the increasing prevalence of cardiovascular risk factors, the disease load of coronary heart disease (CHD) will grow dramatically in the future[1,2]. According to recent European guidelines on myocardial revascularisation, 12 months of dual antiplatelet therapy (DAPT) is generally recommended after patients' drug-eluting stent (DES) implantation[3]. Despite conclusive evidence on the effectiveness of DAPT demonstrated in previous studies[4,5], approximately 9.8% of patients discontinue antiplatelet therapy themselves during the year-1 follow-up period, and the overall discontinuation rate is as high as 23.3%[6]. DAPT discontinuation can lead to higher risks of major adverse cardiovascular events (MACEs)[7], while medication adherence improvement can reduce such risks[8,9].

Mobile health offers new and low-cost approaches for improving patient management of chronic diseases[10,11]. Previous studies have proven that interventions, such as patient

education, counselling and medication reminders, can improve patients' medication adherence as well as outcomes[12,13]. However, few studies have focused on improving patients' DAPT adherence following drug-eluting stent (DES) implantation via social media, especially WeChat. Most of these studies did not provide counselling. Therefore, we designed this multicentre, double-blind, randomised study to explore the prevalence of DAPT discontinuation and the effect of using social media on DAPT adherence among patients who need 1 year of DAPT following their DES implantation.

Methods

Study Design

This WeChat study is a multicentre, double-blind, randomised controlled trial that will include five public hospitals as recruitment sites in Guangdong Province（Figure 1). Participants will be allocated randomly to two arms: the intervention group and the control group. The control group will receive messages four times a week only, while the intervention group will receive interactive responses, medication reminders, medical knowledge education, and follow-up reminders, in addition to messages. Blinding will be maintained during the entire study. Trained research nurses will conduct the follow-ups after 6 and 12 months by telephone or in face-to-face visits. All adverse events will be collected in the self-reported section of the mobile health tool.

Data Collection

Patients in both the intervention and control group will be required to provide baseline information, including social demographic characteristics, history of disease and social behavioural characteristics, such as smoking status and sports activity. They will also be required to use the applet as soon as they are enrolled in the study. They will undergo visits at 6 and 12 months during the 12 months of the follow-up.

Study Population

Participants will meet the following inclusion criteria:

(1) Patients aged ⩾ 18 years undergoing DES implantation within 7 days of recruitment.

(2) Participating patients will receive a recommendation to undergo DAPT for at least 1 year after their doctor's evaluation. Participants with a confirmed diagnosis of ACS will be eligible for the study. The duration of DAPT will be evaluated by Precise-DAPT scores in patients with stable CAD. Those who are recommended to have 12 months of DAPT will also be considered for inclusion.

(3) Participants are required to be WeChat and smartphone users.

(4) Written informed consent will be obtained.

Patients will be excluded for the following reasons: pregnancy; malignant tumour or end-stage disease with a life expectancy of <1 year; prescription for a shorter course of DAPT at discharge; refusal to use social media; and refusal to provide written informed consent for this study.

All patients will receive training on using the app when they enrolled. They will receive a brochure on using the applet and staff guidance. All patients assigned to the intervention group will receive personalised social media interventions four times a week.

Randomisation and Blinding

Randomisation will be performed using a centralised, computerised randomisation program in a uniform 1:1 allocation ratio. The intervention program will be initiated after patients have been enrolled. The patients (but not their care providers), research personnel and investigators will be unaware of their allocation. The study coordinators and research assistants conducting the assessments and the statisticians will also be blinded. This randomisation program is electronically linked to the applet delivering the interactive responses and messages, thereby minimising the need for human interference. Key participant characteristics that will determine intervention

customisation and personalisation will also be automatically imported into the applet administering the intervention.

The Control Group

The control group will receive standard care as determined by their usual doctors. Typical secondary prevention cardiovascular medications include antithrombotic drugs, β-blockers, statins, and angiotensin-converting enzyme inhibitor (ACEIs)/angiotensin II receptor blockers (ARBs). Control group patients will receive messages four times a week, including cardiovascular knowledge and follow-up reminders, such as risk factors for CHD and typical symptoms of myocardial infarction[13]. These patients will have follow-up visits after 6, and 12 months, and they will undergo a physical examination, lifestyle assessment, drug adherence status evaluation, and therapy adjustment. In order to balance the potential influence by social media, controls will also receove the educational material[14].

The Intervention Group

The intervention group will receive the usual messages (eTable1 in the Supplement) with additional personalised reminders that will include a series of messages focusing on medication adherence. They will also receive auto-responses and backstage counselling over the 12-month study period as detailed below.

The interventions for this group are listed but not limited to the following points:

1) Medication Reminders

1. Patients' personal information will be assessed when they are enrolled. The mHealth tool will provide special interventions according to the patients' medical history. Patients who smoke will be advised to quit smoking. Every patient will receive a health report monthly, which will reflect their drug compliance, blood pressure, heart rate, low-density lipoprotein cholesterol level and smoking status.

2. Patients' medication information will be recorded by obtaining pictures of their medication. Patients will be asked to use the punch time clock in the mHealth tool. If

they forget to punch in, they can do so whenever they think of it. If there is no record of medication for 3 days, the intervention group patients will receive SMS alerts and phone over 7 days.

2) Interactive Responses

1. Auto-Response: After sending personal or discomfort symptom questions, patients will be provided with an automatic response pushed by the back-end database that crawls the keywords. The tool suggests that the answer is just for reference. If the intervention group patients have urgent questions, they will be advised to consult their clinicians.

2. The researchers will communicate with the patients once a month. If there is an emergency message, the applet will remind the patient to go to the hospital for immediate treatment/first aid.

Follow-Up

Blood pressure, heart rate, heart rhythm, body weight, lifestyle assessment findings, medication and medication adjustment will be recorded at 6 and 12 months after enrolment. The patients' medication adherence will be evaluated by the proportion of days covered (PDC) according to their prescriptions. MACEs will include all-cause mortality, rehospitalisation, target vessel revascularisation and stroke. The research staff will carefully collect all information through outpatient/telephone call follow-ups.

Timeline

2018/06/01 – 2018/09/30 Ethical application for research proposal is approved by the Institutional Review Board of Guangdong Provincial People's Hospital Ethics Research Committee

2018/10/01 – 2018/12/31 Mobile health tools are developed in collaboration with relevant technology companies. A pilot phase takes place in 36 patients for design optimisation.

2019/01/01 – 2020/12/31 Enrolment is to be completed over 24 months, and at least 760 patients are to be randomly allocated to the control group or the intervention group.

2021/12/01 – 2022/01/01 Follow-up and interim analysis are performed.

Figure 1. Flowchart of study design

DAPT: Dual Antiplatelet Drug

DES: Drug-eluting stent

Study Endpoints

1) Primary Outcome

The primary endpoint will be the discontinuation of any antiplatelet drug within 1 year of DES implantation. The discontinuation duration will be further segmented into periods after the index disruption event, i.e., brief (1–7 days), temporary (8–30 days) and permanent (>30 days), according to follow-ups and records of medication adherence in the applet.

2) Key Secondary Outcomes

The secondary endpoints will be as follows:

1. Medication Adherence: We will assess the patients' DAPT adherence according to PDC by prescription.

2. MACEs, including all-cause mortality, target vessel revascularisation, nonfatal myocardial infarction and stroke.

Definition

9

DAPT is defined as the combination of aspirin and an oral inhibitor of the P2Y12 receptor for adenosine 5'-diphosphate[15].

Oral inhibitors of the P2Y12 receptor include ticagrelor and clopidogrel[16]. Other drugs, such as prasugrel, will not be included because they are not yet available in the Chinese market.

Medication change will be defined as any modification between ticagrelor and clopidogrel under doctors' advice (Table 1).

Table.1 Outcome Definitions

Term	Definition
Dual antiplatelet drug discontinuation	Discontinuation of any dual antiplatelet drug owing to patients' discretion, including bleeding or non-compliance, rather than doctors' advice. Changing of DAPT medication between ticagrelor and clopidogrel under doctors' advice will not be identified as dual antiplatelet drug discontinuation; such changing at patients' discretion will be identified as such [6]
Dual antiplatelet drug disruption	Temporary discontinuation of antiplatelet treatment owing to surgical necessity with reinstitution of DAPT within 14 days [6]
Dual antiplatelet drug discontinuation duration	Is further divided into brief (1–7 days), temporary (8–30 days) and permanent (>30 days)[6]
Medication adherence	Is further divided into poor (PDC<40%), moderate (40-80%) and good (PDC>80%) based on the number of days the patients take their medicine[6]
All-cause mortality	Any death recorded between the date of enrolment and the end of data linkage

Target vascular revascularisation	Any revascularisation procedure (PCI or CABG) involving the vessel treated during the index PCI procedure
Non-fatal myocardial infarction	Typical rise and fall of biochemical markers of myocardial necrosis to greater than twice the ULN; or, if markers are already elevated, further elevation of a marker to >50% of a previous value that had been decreasing, and >2 × ULN, with ⩾1 of the following: 1) ischemic symptoms, 2) development of new pathologic Q waves, 3) ECG changes of new ischemia or 4) pathologic evidence of MI [3]
Stroke	The presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting >24 h. It is strongly recommended (but not required) that an imaging procedure, such as computed tomography or magnetic resonance imaging, be performed.
Major adverse cardiovascular events	The composite of all-cause mortality, target vessel revascularisation, nonfatal myocardial infarction and stroke

Reporting and Evaluating Clinical Adverse Events

The researchers at each centre will carefully observe the main clinical adverse events that occur during the clinical study. They will query and inspect them carefully according to the 'Clinical Incident Registration Form'. They will fill out the 'Clinical Event Registration Form' in the Case Report Form and save all relevant clinical data. Clinical data related to clinical adverse events will be reported to the Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Institute of Cardiovascular Diseases and the subcentre's clinical event committee for assessment. At least two specialist clinicians will be required for confirmation. Any symptoms of discomfort will be self-reported via social media.

Data and Safety Monitoring Board

A committee of clinicians and a biostatistician will periodically review and evaluate the accumulated study data for participants' safety, progress (if appropriate) and efficacy. They will make recommendations to the principal investigators concerning the continuation, modification of enrolment, or termination of the trial. The hospital's academic committee has approved the study design. Confidentiality agreements have been signed with third-party companies.

Ethics and Dissemination

This study will follow the principles of the Good Clinical Practice (GCP) and the Helsinki Declaration. Before the trial begins, the PI at each sub-centre will be responsible for submitting the necessary information, such as the research plan and informed consent documents to the ethics committee for review. It will be the responsibility of the investigator to explain the study's purpose, methodology, benefits and potential adverse events of the interventions. All enrolled patients will be required to provide written, informed consent to participate in this study. The investigator must obtain informed consent from the legal parent or legal guardian of patients who are unable to make a legally binding decision for any reason. Guangdong Provincial People's Hospital's institutional ethics review board has approved the study's design.

Statistical Analysis

The sample size calculation will be based on a previous study[6]. With a test level of 0.05, test efficiency of 80%, 1-year incidence rate in the control group of 24%, 1-year incidence rate in the test group of 15%, significance level of 0.05, power of 80% and dropout rate of <20%,and a two-sided chi-square test, 380 subjects will be required in each group. A total of 760 patients will be needed in the two groups.

Comparisons between normally distributed continuous variables, expressed as means ± standard deviations, will be performed using two-sample *t*-tests. Non-normally distributed continuous variables, presented as medians and interquartile ranges, will be analysed using Wilcoxon rank-sum tests. Pearson chi-square or Fisher' exact tests will be used, as appropriate, for categorical data, which will be expressed as

percentages. The primary and secondary endpoints will be analysed in accordance with the intention-to-treat principle. All tests will be two-tailed, and a p-value of <0.05 will be considered statistically significant. To account for group effects and correct baseline characteristics, the primary endpoint will be compared using a generalised assessment equation, and the SAS version 9.3 will be employed for all analyses. Subgroups will also be analysed, such as age, education level and socioeconomic status, using logistic regression models with the intervention group.

Patient and Public Involvement

Patients and the public were not involved in the design of the study, including the development of the research question, outcomes measures, recruitment to or conduct of the study. The results of the study will be disseminated to the public as deemed appropriate by public health officials.

Discussion

We hypothesise that social media interventions will yield better DAPT adherence in patients with CHD who undergo DES implantation within 1 year.

Despite conclusive evidence on the effectiveness of DAPT, DAPT discontinuation frequently occurs for various reasons, which can lead to many adverse outcomes. Mehran et al[6] enrolled 5018 patients who underwent percutaneous coronary intervention and found that approximately 14.4% of patients discontinued antiplatelet therapy by themselves owing to bleeding or poor adherence during the 2-year follow-up period. The incidence of MACE, stent thrombosis and re-infarction increased significantly in the drug discontinuation group compared with that in the drug continuation group. Improving medication adherence has shown important effects on the long-term prognosis of patients with CHD[17,18].

Previous studies have shown that using mobile medical interventions, even with simple methods, can improve patients' lifestyle and risk factors (eTable2 in the Supplement). The SimCard Trial[19] has shown that patient management with the use of

social media can improve the blood pressure control rate in Asians. It provided evidence that smartphones can promote multifactorial interventions for secondary prevention of CHD. The TEXT ME study[12], a randomised controlled trial with 6 months of follow-up, enrolled 710 patients with CHD. The intervention group received four messages per week, which included four aspects: smoking intervention, diet, physical activity and general coronary health education. Conversely, the control group received standard care only. The intervention group's low-density lipoprotein cholesterol level, systolic blood pressure and body mass index significantly improved. The TEXT ME study occurred in a single centre and had only 6 months of follow-up; nevertheless, it provided a good model for other mobile-based intervention research and design involving social media.

Although the concept of social media-based interventions is not new, it may be a good method for promoting medication adherence, considering the rapidly increasing application ratio of smartphones[20-23]. After analysing our previous questionnaire and investigating the current chronic disease management software on the market, the project's clinical and academic teams and the collaborating technology company jointly developed a CHD management program, which has been internally verified and externally qualified. Rather than creating a brand-new application, our applet is based on WeChat, which has approximately 700 million active users. Our applet will intervene in the patients and their families in various aspects: lifestyle, health education, self-management, supervision, behavioural and medical consultation and treatment adherence evaluation, all of which are associated with improvement in communication efficiency and patient compliance.

In conclusion, we designed this double-blind, multicentre, randomised study to explore whether a social media-based intervention would be effective in enhancing DAPT compliance across multiple hospitals among patients with CHD who have undergone DES implantation within 1 year.

Contributors: LY and CJY had the original idea. SGL,LL CSQ, LJ, HYB,GZD and LLW contributed to the study design. CSQ and LJ were involved in the design of the statistical analysis approach. HYB,GZD,DXH,HLH were involved in literature review

and developing study instruments and materials. YJF, LY, CGQ, and YZH are site PI participated in conducting the trial and acquisition of data. LY, SGL,LL and LLW drafted and revised the manuscript. All authors contributed critical intellectual input and approved the final manuscript.

Funding: The study was supported by grants from the major funding bodies, the Guangdong Provincial People's Hospital Clinical Research Fund (2014dzx02.), Cardiovascular Research Foundation Project of the Chinese Medical Doctor Association (SCRFCMDA201216) and CS Optimizing Antithrombotic Research Fund(BJUHFCSOARF201801-10).

Competing interests: None declared.

Ethics approval: This study was conducted with the approval of the Institutional Review Board of Guangdong Provincial People's Hospital Ethics Research Committee and all other participating sites.

Provenance and peer review: Not commissioned; externally peer-reviewed.

REFERENCE

1. Lin JS, Evans CV, Johnson E,*et al*. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2018;32:281-97.

2. Writing Group M, Mozaffarian D, Benjamin EJ, *et al*. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133:e38-360.

3. Neumann FJ, Sousa-Uva M, Ahlsson A, *et al*. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

4. Ferrieres J, Lautsch D, Ambegaonkar BM, et al. Use of guideline-recommended management in established coronary heart disease in the observational DYSIS II study. *Int J Cardiol*. 2018;270:21-7.

5. Kedhi E, Fabris E, van der Ent M, *et al*. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ.* 2018;363:k3793.

6. Mehran R, Baber U, Steg PG, *et al*. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *The Lancet*. 2013;382:1714-22.

7. Cutlip DE, Kereiakes DJ, Mauri L, *et al*. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv.* 2015;8:404-10.

8. Irvin MR, Shimbo D, Mann DM, *et al*. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich).* 2012;14:694-700.

9. Durand H, Hayes P, Morrissey EC, *et al*. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. *J Hypertens*. 2017;35:2346-57.

10. Patel R, Chang T, Greysen SR, *et al*. Social Media Use in Chronic Disease: A Systematic Review and Novel Taxonomy. *Am J Med.* 2015;128:1335-50.

11. Redfern J, Ingles J, Neubeck L, *et al*. Tweeting our way to cardiovascular health. *J Am Coll Cardiol*. 2013;61:1657-8.

12. Chow CK, Redfern J, Hillis GS,*et al.* Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. *JAMA.* 2015;314:1255-63.

13. Widmer RJ, Allison TG, Lerman LO,*et al*. Digital Health Intervention as an Adjunct to Cardiac Rehabilitation Reduces Cardiovascular Risk Factors and Rehospitalizations. *J Cardiovasc Transl Res*. 2015;8:283-92.

14. Nolan R, Liu S, Feldman R, *et al*. Reducing risk with e-based support for adherence to lifestyle change in hypertension (REACH): protocol for a multicentred randomised controlled trial. *BMJ Open*,2013; 3: e003547.

15. Costa F,Van K D, Feres F,*et al*. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol*.2019;73: 741-754.

16. Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39:213-60.

17. Blasco A, Carmona M, Fernandez-Lozano I, *et al*. Evaluation of a telemedicine service for the secondary prevention of coronary artery disease. *J Cardiopulm Rehabil Prev.* 2012;32:25-31.

18. Reid RD, Morrin LI, Beaton LJ, *et al*. Randomized trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. *Eur J Prev Cardiol*. 2012;19:1357-64.

19. Tian M, Ajay VS, Dunzhu D, et al. A Cluster-Randomized, Controlled Trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular

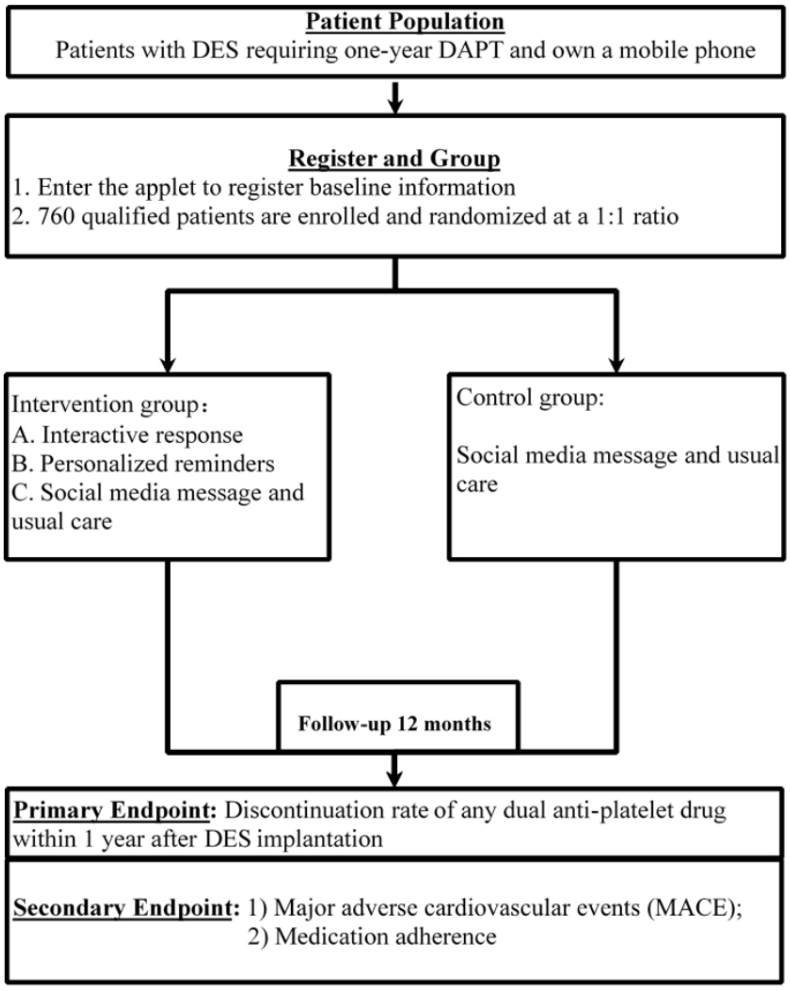
Risk (SimCard Trial) in Rural Tibet, China, and Haryana, India. *Circulation*. 2015; 132:815-24.

20. Vinogradova Y, Coupland C, Brindle P, *et al*. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. *BMJ*. 2016;353:i3305.

21. Santo K, Hyun K, de Keizer L, *et al*. The effects of a lifestyle-focused text-messaging intervention on adherence to dietary guideline recommendations in patients with coronary heart disease: an analysis of the TEXT ME study. *Int J Behav Nutr Phys Act*. 2018;15:45.

22. Dorje T, Zhao G, Scheer A, *et al*. SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol. *BMJ Open*. 2018;8:e021908.

23. Neubeck L, Lowres N, Benjamin EJ, *et al*. The mobile revolution--using smartphone apps to prevent cardiovascular disease. *Nat Rev Cardiol*. 2015;12:350-60.



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Supplement

Table1. Examples of messages

Control Group	Intervention Group (besides *social media messages*)
Social media messages Severe atherosclerosis of the coronary artery results in an insufficient supply of blood to the coronary artery, leading to myocardial ischemia and hypoxia. People who are anxious in mental activity and engage less in physical work are susceptible to coronary heart disease. Smoking can increase the risk of coronary atherosclerosis and stroke.	*Personalized reminder* *-For patients with diabetes* -It is recommended that you check your blood glucose regularly. -Did your blood glucose meet the requirements today? *Medication reminder* -Aspirin helps to prevent plaque formation. Please taking aspirin once per day. -Did you take your antiplatelet drugs today? *For patients with hypertension* -Your blood pressure is a little high today; please continue to monitor it.
	Interactive responses (crawling the keywords) -Asked by users: What can people with coronary heart disease eat? -Auto-response: Eat: food with low salt and fat.

	-Asked by users: How to deal with a stomach-ache after taking medicine -Auto-response: Stomach-ache: If there is an emergency, please go to the hospital for immediate treatment/first aid.

Table 2 Characteristics of randomized controlled trials with intervention to improve patients' lifestyle among patients with coronary heart disease

Study	Design	Duration	Population	Primary endpoint & Secondary endpoint	Experimental group vs Control group
Karla et al 2018[1]	RCT	3months	163 patients with CHD	Drug adherence (MMAS-8 score) &Blood pressure and cholesterol levels	**Intervention group** Basic APP:alarm Advanced APP:record and snooze the pause **Control group** -usual medical care
Salvi et al, 2018[2]	RCT	24 months	118 patients with MI	Education level about heart-related health improve more in the intervention groups(p=0.01). Exercise habits improved without	**Intervention group** -the mobile station: a wearable sensor capable with app -the patient station: feedback and educational information -the professional station: monitor patients and generates alerts

				statistical significance.	**Control group** -receiving standard rehabilitation
Bravo-Escobar et al, 2018[3]	RCT	2 months	28 patients with stable CHD at Moderate cardiovascular risk	Exercise time. & quality of life score	**Intervention group** -hospital exercise once a week -exercised at home following a program monitored with a remote electrocardiographic device **Control group** -hospital exercise 3 times a week -encourage to do exercise at home
Clara et al, 2016 [4]	RCT	6months	710 patients with CHD	LDLC &Systolic blood pressure, body mass index (BMI), physical activity, and smoking status.	**Intervention group** -TM providing lifestyle advice ,motivational reminders, and support to change lifestyle behaviors.(four times a week) -usual medical care **Control group**

					-usual medical care
Linda et al, 2015[5]	RCT	30 days	90 patients with CHD	There was no significant difference in the improvement as a function of the different treatment groups (F (2,6.24) =0.45, p=0.64).	**TM Reminders+ TM Education group** -two-way reminders messages on drug -one-way health messages **TM Education group** -one-way health messages **Control group** -Usual care/No TM
Leila et al, 2015[6]	RCT	6 months	123 patients with CHD	The intervention group reported significantly greater medication adherence score (mean difference: 0.58, 95% CI 0.19-0.97; P=.004).	**Intervention group** -24 week text message program and access to website -Standard CR services -3-month phone call **Control group** -Standard CR services -3-month phone call

Vernooij et al, 2012[7]	RCT	12 months	330 patients with atherosclerosis.	A relative change of -12% (-22% to -3%) in Framingham heart risk score for the intervention group compared with the usual care group	**Intervention group** -Personalized website -Nurse reminder **Usual care group** -Usual care by doctor
Blasco et al, 2012[8]	RCT	12 months	203 patients with ACS	Telemonitoring group experience improvement in cardiovascular risk factors profile than control patients (RR 1.4;95% CI 1.1-1.7)	**Telemonitoring group** -health data website -health recommendation messages -lifestyle counseling -usual-care treatment **Control group** -lifestyle counseling -usual-care treatment
Reid et al, 2012[9]	RCT	6 months	223 patients after PCI without	Emotional ($p<0.038$) and physical ($p<0.031$) dimensions of	**Intervention group** -6-month online tutorials -feedback email

	enrolling in cardiac rehabilitation.	heart disease health-related quality of life were higher in CardioFit group.	**Control group** -physical activity guidance from doctors and book

RCT=randomized controlled trial

TM=text messages

CR=cardiac rehabilitation

1. Santo K, Singleton A, Rogers K, *et al*. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial.*Heart.* 2018.10.1136/heartjnl-2018-313479

2. Salvi D, Ottaviano M, Muuraiskangas S, Martinez-Romero A, Vera-Munoz C, Triantafyllidis A, et al. An m-Health system for education and motivation in cardiac rehabilitation: the experience of HeartCycle guided exercise. J Telemed Telecare. 2018;24(4):303-16.

3. Bravo-Escobar R, Gonzalez-Represas A, Gomez-Gonzalez AM, *et al*. Effectiveness and safety of a home-based cardiac rehabilitation programme of mixed surveillance in patients with ischemic heart disease at moderate cardiovascular risk: A randomised, controlled clinical trial. *BMC Cardiovasc Disord*. 2017;17(1):66.

4. Chow CK, Redfern J, Hillis GS,*et al.* Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With

Coronary Heart Disease: A Randomized Clinical Trial. *JAMA.* 2015;314:1255-63.

5. Park LG, Howie-Esquivel J, Whooley MA, *et al*. Psychosocial factors and medication adherence among patients with coronary heart disease: A text messaging intervention. *Eur J Cardiovasc Nurs*. 2015;14:264-73.

6. Pfaeffli Dale L, Whittaker R, Jiang Y, *et al*. Text Message and Internet Support for Coronary Heart Disease Self-Management: Results From the Text4Heart Randomized Controlled Trial. *J Med Internet Res*. 2015;17:e237.

7. Vernooij JW, Kaasjager HA, van der Graaf Y, *et al*. Internet based vascular risk factor management for patients with clinically manifest vascular disease: randomised controlled trial. *BMJ.* 2012;344:e3750.

8. Blasco A, Carmona M, Fernandez-Lozano I, *et al*. Evaluation of a telemedicine service for the secondary prevention of coronary artery disease. *J Cardiopulm Rehabil Prev.* 2012;32:25-31.

9. Reid RD, Morrin LI, Beaton LJ, *et al*. Randomized trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. *Eur J Prev Cardiol*. 2012;19:1357-64.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title（P1）	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P1)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P15)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P15)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale(P4)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

Trial design(P4)	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting (P4)	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria (P6)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions (P7)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes(P9)	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline(P8)	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size(P13)	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation(P7)	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)(P6)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods(P5)	18a	Plans for assessment and collection of outcome, baseline, 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
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management (P13)	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods(P13)	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring(P12)	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval (P12)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent (P13)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests (P15)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy (P14)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Rationale and design of the Web basEd soCial media tecHnology to improvement in Adherence to dual anTiplatelet Therapy following Drug-Eluting Stent Implantation(WECHAT): protocol for a randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033017.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Nov-2019
Complete List of Authors:	Sun, Guo-li; Guangdong Cardiovascular Institute, cardiology; South China University of Technology, Lei, Li; Guangdong General Hospital Liu, Liwei; Southern Medical University, The Second School of Clinical Medicine Liu, Jin; Guangdong General Hospital, He, Yibo; Guangdong Cardiovascular Institute, Guo, Zhaodong; Guangdong General Hospital dai, xiaohua; Guangdong Cardiovascular Institute; School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, 510000, Guangdong, China He, Lihao; Guangdong General Hospital Chen, Shi-qun; Guangdong Cardiovascular Institute, Guangdong provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Cardiology Liang, Yan; Department of Cardiology, Maoming People's Hospital, Maoming, Guangdong,525000 China Ye, Jianfeng; Dongguan People's Hospital Hu, Yunzhao; First People's Hospital Chen, Guoqin; Guangzhou Panyu Central Hospital, Guangzhou, China., Cardiology Chen, Ji-yan; Guangdong Cardiovascular Institute, Guangdong provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Cardiology Liu, Yong; Guangdong Cardiovascular Institute, ; South China University of Technology,
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical management
Keywords:	Mobile health, Discontinuation rate, Dual antiplatelet therapy

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Rationale and design of the Web basEd soCial media tecHnology to improvement in Adherence to dual anTiplatelet Therapy following Drug-Eluting Stent Implantation(WECHAT): protocol for a randomised controlled study

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Conflicts of Interest: None.

Abstract

Background: Dual antiplatelet therapy (DAPT) is frequently discontinued after drug-eluting stent (DES) implantation, which could increase the risk of major adverse cardiovascular events (MACEs). Few studies have attempted to improve DAPT adherence through web-based social media.

Objective: To explore the effect of social media on DAPT adherence following DES implantation.

Methods/Design: The WeChat trial is a multicentre, double-blind, randomised study (1:1). It will recruit 760 patients with DES who require 12 months of DAPT. The control group will only receive usual care and general educational messages on medical knowledge. The intervention group will receive a personalised intervention, including interactive responses and medication and follow-up reminders beyond the general educational messages. The primary endpoint will be the discontinuation rate which is defined as the cessation of any dual antiplatelet drug owing to the participants' discretion within one year of DES implantation. The secondary endpoints will include medication adherence and major adverse cardiovascular events (MACE). Both groups will receive messages or reminders four times a week with follow-ups over 12 months.

Ethics and Dissemination: Ethical approval was granted by Ethics Committee of Guangdong Provincial People's Hospital(GDREC2018327H). Results will be disseminated via peer-reviewed publications and presentations at international conferences.

Trial registration: ClinicalTrials.gov. NCT03732066

Keywords: Mobile health, Drug-Eluting Stents, Dual Antiplatelet Therapy, Randomised Controlled Trial

Strengths and limitations of this study:

1. This multicentre trial will firstly provide comprehensive evidence of the effectiveness of social media on drug compliance with dual antiplatelet therapy and health management.

2. Interactive response based on behaviour change theory will offer a new approach for motivating patient stickiness and obtaining patient feedback.

3. The distribution of people older than 65 years may be limited because the study requires the use of smartphones

4. The causes of discontinuation of either drug, such as drug changes, gastrointestinal reactions and allergies to aspirin, could not be collected and classified.

Introduction

With an aging population and the increasing prevalence of cardiovascular risk factors, the disease load of coronary heart disease (CHD) will grow dramatically in the future[1,2]. Dual antiplatelet therapy (DAPT) is generally recommended after patients' drug-eluting stent (DES) implantation to reduce cardiac events[3]. Despite conclusive evidence on the effectiveness of DAPT demonstrated in previous studies[4,5], approximately 9.8% of patients discontinue antiplatelet therapy themselves during the one-year follow-up period, and the overall discontinuation rate is as high as 23.3%[6] in the USA and Europe. The discontinuation in one year is higher than that in the short duration. The incidence of major adverse events (MACE), stent thrombosis, and target vessel revascularization was significantly increased in patients with DAPT cessation due to poor adherence[6,7]. Many studies have demonstrated that improving medication adherence is of great significance for the long-term prognosis of patients with cardiovascular diseases[8,9].

Mobile health offers new and low-cost approaches for improving patient management of chronic diseases[10,11]. Previous studies have proven that interventions, such as patient education, counselling and medication reminders, can improve patients' medication adherence as well as outcomes[12,13]. However, only several studies have focused on

improving patients' DAPT adherence via social media, especially the popolar application WeChat. Therefore, we designed this multicentre, double-blind, randomised study to explore the prevalence of DAPT discontinuation and the effect of social media on DAPT adherence among patients who need one year of DAPT following their DES implantation.

Methods

Study Design

This WeChat study is a multicentre, double-blind, randomised controlled trial that will include five public hospitals as recruitment sites in Guangdong Province. Participants will be allocated randomly to two arms: the intervention group and the control group. The control group will receive messages four times a week only, while the intervention group will receive interactive responses, medication reminders, medical knowledge education, and follow-up reminders, in addition to messages. Blinding will be maintained during the entire study(Figure 1). Trained research nurses will conduct the follow-ups after 6 and 12 months by telephone or in face-to-face visits. All adverse events will be collected in the self-reported section of the mobile health tool or by the investigators.

Data Collection

Patients in both groups will be required to provide baseline information, including social demographic characteristics, history of diseases and social behavioural characteristics, such as smoking status and sports activity. They will also be required to use Wechat as soon as they are enrolled in the study. Medication adherence will be evaluated by the proportion of days covered (PDC) at both 6-month and 12-month visits.

Study Population

Participants will meet the following inclusion criteria:

(1) Patients aged ≥18 years undergoing DES implantation within 7 days of recruitment.

(2) Participating patients are required to receive a recommendation to undergo DAPT for at least 1 year after their doctor's evaluation. Participants with a confirmed diagnosis of ACS will be eligible for the study. The duration of DAPT will be evaluated by Precise-DAPT scores and in patients with stable CAD. Those who are recommended to have 12 months of DAPT will also be considered for inclusion.

(3) Participants are required to be WeChat and smartphone users.

(4) Written informed consent will be obtained.

Patients will be excluded for the following reasons: pregnancy; malignant tumour or end-stage disease with a life expectancy of <1 year; prescription for a shorter course of DAPT at discharge; refusal to use social media; refusal to provide written informed consent for this study.

All patients will receive training on using the app when they enrolled. They will receive a brochure on using the applet and staff guidance. All patients assigned to the intervention group will receive personalised social media interventions four times a week.

Randomisation and Blinding

Randomisation will be performed using a centralised, computerised randomisation program in a uniform 1:1 allocation ratio. The intervention program will be initiated after patients have been enrolled. The patients (but not their care providers), and research personnel will be unaware of their allocation. The study coordinators and research assistants conducting the assessments and the statisticians will also be blinded. This randomisation program is electronically linked to the applet delivering the interactive responses and messages, thereby minimising the need for human interference. Key participant characteristics that will determine intervention customisation and personalisation will also be automatically imported into the applet administering the intervention.

The Control Group

The control group will receive standard care as determined by their usual doctors. Typical secondary prevention cardiovascular medications include antithrombotic drugs, β-blockers, statins, and angiotensin-converting enzyme inhibitor (ACEIs)/angiotensin II receptor blockers (ARBs). Control group patients will receive messages four times a week, including cardiovascular knowledge and follow-up reminders, such as risk factors for CHD and typical symptoms of myocardial infarction[13]. These patients will have follow-up visits after 6, and 12 months, and they will undergo a physical examination, lifestyle assessment, drug adherence status evaluation, and therapy adjustment. In order to balance the potential influence by social media, controls will also receive the educational material[14].

The Intervention Group

The intervention group will receive the usual messages (eTable1 in the Supplement) with additional personalised reminders that will include a series of messages focusing on medication adherence. They will also receive auto-responses and backstage counselling over the 12-month study period as detailed below.

The interventions for this group are listed but not limited to the following points:

1) Medication Reminders

1. Patients' personal information will be assessed when they are enrolled. The mHealth tool will provide special interventions according to the patients' medical history. For example, patients who smoke will be advised to quit smoking. Every patient will receive a health report monthly, which will reflect their drug compliance, blood pressure, heart rate, low-density lipoprotein cholesterol level and smoking status.

2. Patients' medication information will be recorded by obtaining pictures of their medication. Patients will be asked to use the punch time clock in the mHealth tool. If they forget to punch in, they can do so whenever they think of it. If there is no record of medication for 3 days, the intervention group patients will receive SMS alerts and

phone over 7 days.

2) Interactive Responses

1. Auto-Response: After sending personal or discomfort symptom questions, patients will be provided with an automatic response pushed by the back-end database that crawls the keywords. The tool suggests that the answer is just for reference. If the intervention group patients have urgent questions, they will be advised to consult their clinicians.

2. The researchers will communicate with the patients once a month. If there is an emergency message, the applet will remind the patient to go to the hospital for immediate treatment/first aid.

Follow-Up

Blood pressure, heart rate, heart rhythm, body weight, lifestyle assessment findings, medication and medication adjustment will be recorded at 6 and 12 months after enrolment. The patients' medication adherence will be evaluated by PDC according to their prescriptions. Major adverse cardiac events(MACEs) will include all-cause mortality, rehospitalisation, target vessel revascularisation and stroke. The research staff will carefully collect all information through outpatient/telephone call follow-ups.

Timeline

2018/06/01 – 2018/09/30 Ethical application for research proposal is approved by the Institutional Review Board of Guangdong Provincial People's Hospital Ethics Research Committee

2018/10/01 – 2018/12/31 Mobile health tools are developed in collaboration with relevant technology companies. A pilot phase takes place in 36 patients for design optimisation.

2019/01/01 – 2020/12/31 Enrolment is to be completed over 24 months, and at least 760 patients are to be randomly allocated to the control group or the intervention

group.

2021/12/01 – 2022/01/01 Follow-up and interim analysis are performed.

Figure 1. Flowchart of study design

DAPT: Dual Antiplatelet Drug

DES: Drug-eluting stent

Study Endpoints

1) Primary Outcome

The primary endpoint will be the discontinuation rate of any antiplatelet drug within 1 year of DES implantation. The discontinuation duration will be further segmented into periods after the index disruption event, i.e., brief (1–7 days), temporary (8–30 days) and permanent (>30 days), according to follow-ups and records of medication adherence in the applet[6].

2) Key Secondary Outcomes

The secondary endpoints will be as follows:

1. Medication Adherence: We will assess the patients' DAPT adherence according to PDC by prescription.

2. MACEs, including all-cause mortality, target vessel revascularisation, nonfatal myocardial infarction and stroke.

Definition

DAPT is defined as the combination of aspirin and an oral inhibitor of the P2Y12 receptor for adenosine 5'-diphosphate[15].

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Oral inhibitors of the P2Y12 receptor include ticagrelor and clopidogrel[16]. Other drugs, such as prasugrel, will not be included because they are not yet available in the Chinese market.

Medication change will be defined as any modification between ticagrelor and clopidogrel under doctors' advice (Table 1).

Table.1 Outcome Definitions

Term	Definition
Dual antiplatelet drug discontinuation	Discontinuation of any dual antiplatelet drug owing to patients' discretion, including bleeding or non-compliance, rather than doctors' advice. Changing of DAPT medication between ticagrelor and clopidogrel under doctors' advice will not be identified as dual antiplatelet drug discontinuation; such changing at patients' discretion will be identified as such [6]
Dual antiplatelet drug discontinuation duration	Is further divided into brief (1–7 days), temporary (8–30 days) and permanent (>30 days)[6]
Medication adherence	Is further divided into poor (PDC<40%), moderate (40-80%) and good (PDC>80%) based on the number of days the patients take their medicine[6]
All-cause mortality	Any death recorded between the date of enrolment and the end of data linkage
Target vascular revascularisation	Any revascularisation procedure involving percutaneous coronary intervention(PCI) of the target lesion or surgical bypass of the target vessel
Non-fatal	Typical rise and fall of biochemical markers of myocardial necrosis to

myocardial infarction	greater than twice the ULN; or, if markers are already elevated, further elevation of a marker to >50% of a previous value that had been decreasing, and >2 × ULN, with ≥1 of the following: 1) ischemic symptoms, 2) development of new pathologic Q waves, 3) ECG changes of new ischemia or 4) pathologic evidence of MI [3]
Stroke	The presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting >24 h. It is strongly recommended (but not required) that an imaging procedure, such as computed tomography or magnetic resonance imaging, be performed.

Reporting and Evaluating Clinical Adverse Events

The researchers at each centre will carefully observe the main clinical adverse events that occur during the clinical study. They will query and inspect them carefully according to the 'Clinical Incident Registration Form'. They will fill out the 'Clinical Event Registration Form' in the Case Report Form and save all relevant clinical data. Clinical data related to clinical adverse events will be reported to the Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Institute of Cardiovascular Diseases and the subcentre's clinical event committee for assessment. At least two specialist clinicians will be required for confirmation. Any symptoms of discomfort will be self-reported via social media.

Data and Safety Monitoring Board

A committee of clinicians and a biostatistician will periodically review and evaluate the accumulated study data for participants' safety, progress (if appropriate) and efficacy. They will make recommendations to the principal investigators concerning the continuation, modification of enrolment, or termination of the trial. The hospital's academic committee has approved the study design. Confidentiality agreements have been signed with third-party companies.

Ethics and Dissemination

This study will follow the principles of the Good Clinical Practice (GCP) and the Helsinki Declaration. Before the trial begins, the PI at each sub-centre will be responsible for submitting the necessary information, such as the research plan and informed consent documents to the ethics committee for review. It will be the responsibility of the investigator to explain the study's purpose, methodology, benefits and potential adverse events of the interventions. All enrolled patients will be required to provide written, informed consent to participate in this study. The investigator must obtain informed consent from the legal parent or legal guardian of patients who are unable to make a legally binding decision for any reason. Guangdong Provincial People's Hospital's institutional ethics review board has approved the study's design.

Statistical Analysis

The sample size calculation will be based on a previous study[6]. With a test level of 0.05, test efficiency of 80%, 1-year incidence rate in the control group of 24%, 1-year incidence rate in the test group of 15%, significance level of 0.05, power of 80% and dropout rate of <20%,and a two-sided chi-square test, 380 subjects will be required in each group. A total of 760 patients will be needed in the two groups.

Comparisons between normally distributed continuous variables, expressed as means ± standard deviations, will be performed using two-sample *t*-tests. Non-normally distributed continuous variables, presented as medians and interquartile ranges, will be analysed using Wilcoxon rank-sum tests. Pearson chi-square or Fisher' exact tests will be used, as appropriate, for categorical data, which will be expressed as percentages. The primary and secondary endpoints will be analysed in accordance with the intention-to-treat principle. All tests will be two-tailed, and a p-value of <0.05 will be considered statistically significant. To account for group effects and correct baseline characteristics, the primary endpoint will be compared using a generalised assessment equation, and the SAS version 9.3 will be employed for all analyses. Subgroups will also be analysed, such as age, education level and socioeconomic status, using logistic regression models with the intervention group.

Patient and Public Involvement

Patients and the public were not involved in the design of the study, including the development of the research question, outcomes measures, recruitment to or conduct of the study. The results of the study will be disseminated to the public as deemed appropriate by public health officials.

Discussion

We hypothesise that social media interventions will yield better DAPT adherence in patients with CHD who undergo DES implantation within 1 year.

Despite conclusive evidence on the effectiveness of DAPT, DAPT discontinuation frequently occurs for various reasons, which can lead to many adverse outcomes. Cutlip DE., et al found that incidence of antiplatelet drug cessation was about 9.6% in 2159 patients with DES within 6 months after operation. And the risk of death or recurrent myocardial infarction in those patients with poor compliance was higher (7.6% vs 3.0%, $P < 0.001$)[17]. In Asian, the early discontinuation rate was 31.0%. It seems to be significantly higher than those reported from prospective studies, which may more likely reflect the real-world situation[18].

Previous studies have shown that using mobile medical interventions, even with simple methods, can improve patients' lifestyle and risk factors (eTable2 in the Supplement). The SimCard Trial[19] has shown that patient management with the use of social media can improve the blood pressure control rate in Asians. It provided evidence that smartphones can promote multifactorial interventions for secondary prevention of CHD. The TEXT ME study[12], a randomised controlled trial with 6 months of follow-up, enrolled 710 patients with CHD. The intervention group received four messages per week, which included four aspects: smoking intervention, diet, physical activity and general coronary health education. Conversely, the control group received standard care only. The intervention group's low-density lipoprotein cholesterol level, systolic blood pressure and body mass index significantly improved. The TEXT ME study occurred in a single centre and had only 6 months of follow-up; nevertheless, it provided a good model for other mobile-based intervention research and design involving social media.

Although the concept of social media-based interventions is not new, it may be a good method for promoting medication adherence, considering the rapidly increasing application ratio of smartphones[20-23]. After analysing our previous questionnaire and investigating the current chronic disease management software on the market, the project's clinical and academic teams and the collaborating technology company jointly developed a CHD management program, which has been internally verified and externally qualified. Rather than creating a brand-new application, our applet is based on WeChat, which has approximately 700 million active users. Our applet will intervene in the patients and their families in various aspects: lifestyle, health education, self-management, supervision, behavioural and medical consultation and treatment adherence evaluation, all of which are associated with improvement in communication efficiency and patient compliance.

In conclusion, we designed this double-blind, multicentre, randomised study to explore whether a social media-based intervention would be effective in enhancing DAPT compliance across multiple hospitals among patients with CHD who have undergone DES implantation within 1 year.

Contributors: LY and CJY had the original idea. SGL,LL CSQ, LJ, HYB,GZD and LLW contributed to the study design. CSQ and LJ were involved in the design of the statistical analysis approach. HYB,GZD,DXH,HLH were involved in literature review and developing study instruments and materials. YJF, LY, CGQ, and YZH are site PI participated in conducting the trial and acquisition of data. LY, SGL,LL and LLW drafted and revised the manuscript. All authors contributed critical intellectual input and approved the final manuscript.

Funding: The study was supported by grants from the major funding bodies, the Guangdong Provincial People's Hospital Clinical Research Fund (2014dzx02.), Cardiovascular Research Foundation Project of the Chinese Medical Doctor Association (SCRFCMDA201216) and CS Optimizing Antithrombotic Research Fund(BJUHFCSOARF201801-10).

Competing interests: None declared.

Ethics approval: This study was conducted with the approval of the Institutional Review Board of Guangdong Provincial People's Hospital Ethics Research Committee(GDREC2018327H). Results will be disseminated via peer-reviewed publications and presentations at international conferences.

Provenance and peer review: Not commissioned; externally peer-reviewed.

REFERENCE

1. Lin JS, Evans CV, Johnson E,*et al*. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2018;32:281-97.

2. Writing Group M, Mozaffarian D, Benjamin EJ, *et al*. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133:e38-360.

3. Neumann FJ, Sousa-Uva M, Ahlsson A, *et al*. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

4. Ferrieres J, Lautsch D, Ambegaonkar BM, et al. Use of guideline-recommended management in established coronary heart disease in the observational DYSIS II study. *Int J Cardiol*. 2018;270:21-7.

5. Kedhi E, Fabris E, van der Ent M, *et al*. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ.* 2018;363:k3793.

6. Mehran R, Baber U, Steg PG, *et al*. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *The Lancet*. 2013;382:1714-22.

7. Cutlip DE, Kereiakes DJ, Mauri L, *et al*. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv.* 2015;8:404-10.

8. Irvin MR, Shimbo D, Mann DM, *et al*. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich).* 2012;14:694-700.

9. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA 2007;297:177–86..

10. Patel R, Chang T, Greysen SR, *et al*. Social Media Use in Chronic Disease: A Systematic Review and Novel Taxonomy. *Am J Med.* 2015;128:1335-50.

11. Redfern J, Ingles J, Neubeck L, *et al*. Tweeting our way to cardiovascular health. *J Am Coll Cardiol*. 2013;61:1657-8.

12. Chow CK, Redfern J, Hillis GS,*et al.* Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. *JAMA.* 2015;314:1255-63.

13. Widmer RJ, Allison TG, Lerman LO,*et al*. Digital Health Intervention as an Adjunct to Cardiac Rehabilitation Reduces Cardiovascular Risk Factors and Rehospitalizations. *J Cardiovasc Transl Res*. 2015;8:283-92.

14. Nolan R, Liu S, Feldman R, *et al*. Reducing risk with e-based support for adherence to lifestyle change in hypertension (REACH): protocol for a multicentred randomised controlled trial. *BMJ Open*,2013; 3: e003547.

15. Costa F,Van K D, Feres F,*et al*. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol*.2019;73: 741-754.

16. Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213-60.

17. Cutlip DE, Kereiakes D J, Mauri L, *et al*. Thrombotic Complications Associated With Early and Late Nonadherence to Dual AntiplateletTherapy. *JACC Cardiovasc Interv*. 2015;8:404-10.

18. Cho M H, Shin D W, Yun J M, *et al*. Prevalence and Predictors of Early Discontinuation of Dual-Antiplatelet Therapy After Drug-Eluting Stent Implantation in Korean Population. *Am J Cardiol.* 2016,118:1448-54.

19. Tian M, Ajay VS, Dunzhu D, *et al*. A Cluster-Randomized, Controlled Trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk (SimCard Trial) in Rural Tibet, China, and Haryana, India. *Circulation*. 2015; 132:815-24.

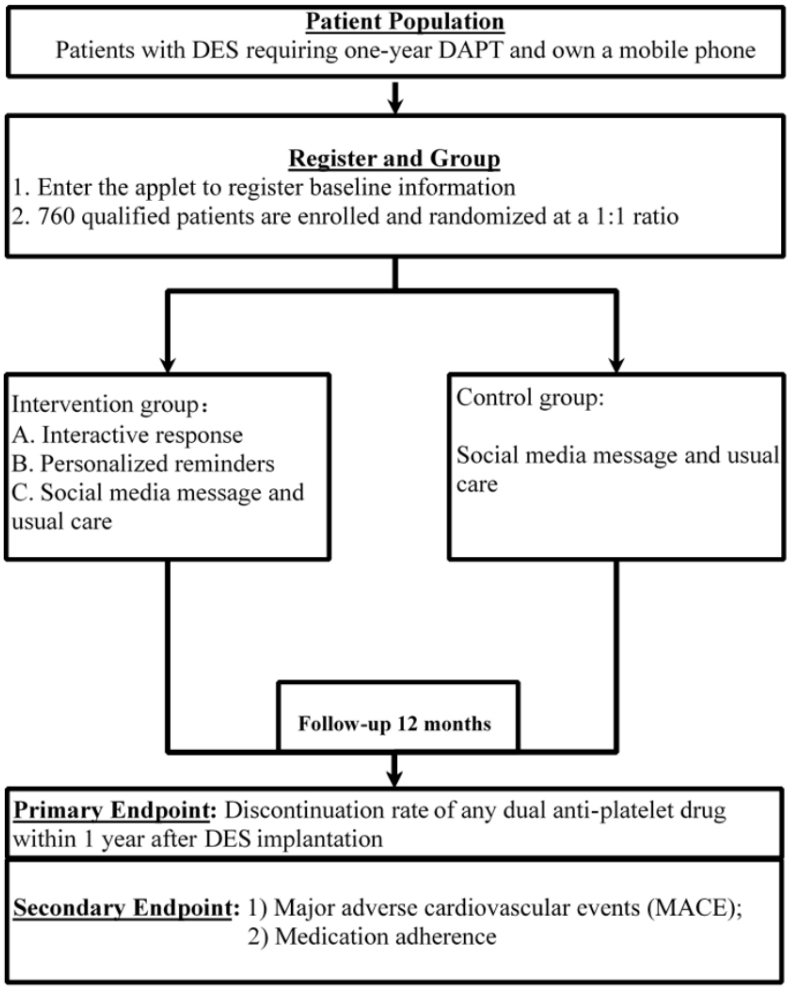
20. Vinogradova Y, Coupland C, Brindle P, *et al*. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. *BMJ*. 2016;353:i3305.

21. Santo K, Hyun K, de Keizer L, *et al*. The effects of a lifestyle-focused text-messaging intervention on adherence to dietary guideline recommendations in patients with coronary heart disease: an analysis of the TEXT ME study. *Int J Behav Nutr Phys*

Act. 2018;15:45.

22. Dorje T, Zhao G, Scheer A, *et al*. SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol. *BMJ Open*. 2018;8:e021908.

23. Neubeck L, Lowres N, Benjamin EJ, *et al*. The mobile revolution--using smartphone apps to prevent cardiovascular disease. *Nat Rev Cardiol.* 2015;12:350-60.



90x90mm (300 x 300 DPI)

Supplement

Table1. Examples of messages

Control Group	Intervention Group (besides *social media messages*)
Social media messages Severe atherosclerosis of the coronary artery results in an insufficient supply of blood to the coronary artery, leading to myocardial ischemia and hypoxia. People who are anxious in mental activity and engage less in physical work are susceptible to coronary heart disease. Smoking can increase the risk of coronary atherosclerosis and stroke.	*Personalized reminder* *-For patients with diabetes* -It is recommended that you check your blood glucose regularly. -Did your blood glucose meet the requirements today? *Medication reminder* -Aspirin helps to prevent plaque formation. Please taking aspirin once per day. -Did you take your antiplatelet drugs today? *For patients with hypertension* -Your blood pressure is a little high today; please continue to monitor it.
	Interactive responses (crawling the keywords) -Asked by users: What can people with coronary heart disease eat? -Auto-response: Eat: food with low salt and fat.

	-Asked by users: How to deal with a stomach-ache after taking medicine -Auto-response: Stomach-ache: If there is an emergency, please go to the hospital for immediate treatment/first aid.

Table 2 Characteristics of randomized controlled trials with intervention to improve patients' lifestyle among patients with coronary heart disease

Study	Design	Duration	Population	Primary endpoint & Secondary endpoint	Experimental group vs Control group
Karla et al 2018[1]	RCT	3months	163 patients with CHD	Drug adherence (MMAS-8 score) &Blood pressure and cholesterol levels	**Intervention group** Basic APP:alarm Advanced APP:record and snooze the pause **Control group** -usual medical care
Salvi et al, 2018[2]	RCT	24 months	118 patients with MI	Education level about heart-related health improve more in the intervention groups(p=0.01). Exercise habits improved without	**Intervention group** -the mobile station: a wearable sensor capable with app -the patient station: feedback and educational information -the professional station: monitor patients and generates alerts

				statistical significance.	**Control group** -receiving standard rehabilitation
Bravo-Escobar et al, 2018[3]	RCT	2 months	28 patients with stable CHD at Moderate cardiovascular risk	Exercise time. & quality of life score	**Intervention group** -hospital exercise once a week -exercised at home following a program monitored with a remote electrocardiographic device **Control group** -hospital exercise 3 times a week -encourage to do exercise at home
Clara et al, 2016 [4]	RCT	6months	710 patients with CHD	LDLC &Systolic blood pressure, body mass index (BMI), physical activity, and smoking status.	**Intervention group** -TM providing lifestyle advice ,motivational reminders, and support to change lifestyle behaviors.(four times a week) -usual medical care **Control group**

					-usual medical care
Linda et al, 2015[5]	RCT	30 days	90 patients with CHD	There was no significant difference in the improvement as a function of the different treatment groups (F (2,6.24) =0.45, p=0.64).	**TM Reminders+ TM Education group** -two-way reminders messages on drug -one-way health messages **TM Education group** -one-way health messages **Control group** -Usual care/No TM
Leila et al, 2015[6]	RCT	6 months	123 patients with CHD	The intervention group reported significantly greater medication adherence score (mean difference: 0.58, 95% CI 0.19-0.97; P=.004).	**Intervention group** -24 week text message program and access to website -Standard CR services -3-month phone call **Control group** -Standard CR services -3-month phone call

Vernooij et al, 2012[7]	RCT	12 months	330 patients with atherosclerosis.	A relative change of -12% (-22% to -3%) in Framingham heart risk score for the intervention group compared with the usual care group	**Intervention group** -Personalized website -Nurse reminder **Usual care group** -Usual care by doctor
Blasco et al, 2012[8]	RCT	12 months	203 patients with ACS	Telemonitoring group experience improvement in cardiovascular risk factors profile than control patients (RR 1.4;95% CI 1.1-1.7)	**Telemonitoring group** -health data website -health recommendation messages -lifestyle counseling -usual-care treatment **Control group** -lifestyle counseling -usual-care treatment
Reid et al, 2012[9]	RCT	6 months	223 patients after PCI without	Emotional ($p<0.038$) and physical ($p<0.031$) dimensions of	**Intervention group** -6-month online tutorials -feedback email

	enrolling in cardiac rehabilitation.	heart disease health-related quality of life were higher in CardioFit group.	**Control group** -physical activity guidance from doctors and book

RCT=randomized controlled trial

TM=text messages

CR=cardiac rehabilitation

1. Santo K, Singleton A, Rogers K, *et al*. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial.*Heart.* 2018.10.1136/heartjnl-2018-313479

2. Salvi D, Ottaviano M, Muuraiskangas S, Martinez-Romero A, Vera-Munoz C, Triantafyllidis A, et al. An m-Health system for education and motivation in cardiac rehabilitation: the experience of HeartCycle guided exercise. J Telemed Telecare. 2018;24(4):303-16.

3. Bravo-Escobar R, Gonzalez-Represas A, Gomez-Gonzalez AM, *et al*. Effectiveness and safety of a home-based cardiac rehabilitation programme of mixed surveillance in patients with ischemic heart disease at moderate cardiovascular risk: A randomised, controlled clinical trial. *BMC Cardiovasc Disord*. 2017;17(1):66.

4. Chow CK, Redfern J, Hillis GS,*et al.* Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With

Coronary Heart Disease: A Randomized Clinical Trial. *JAMA.* 2015;314:1255-63.

5. Park LG, Howie-Esquivel J, Whooley MA, *et al*. Psychosocial factors and medication adherence among patients with coronary heart disease: A text messaging intervention. *Eur J Cardiovasc Nurs*. 2015;14:264-73.

6. Pfaeffli Dale L, Whittaker R, Jiang Y, *et al*. Text Message and Internet Support for Coronary Heart Disease Self-Management: Results From the Text4Heart Randomized Controlled Trial. *J Med Internet Res*. 2015;17:e237.

7. Vernooij JW, Kaasjager HA, van der Graaf Y, *et al*. Internet based vascular risk factor management for patients with clinically manifest vascular disease: randomised controlled trial. *BMJ.* 2012;344:e3750.

8. Blasco A, Carmona M, Fernandez-Lozano I, *et al*. Evaluation of a telemedicine service for the secondary prevention of coronary artery disease. *J Cardiopulm Rehabil Prev.* 2012;32:25-31.

9. Reid RD, Morrin LI, Beaton LJ, *et al*. Randomized trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. *Eur J Prev Cardiol*. 2012;19:1357-64.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description
Administrative information		
Title	1-P1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a-P1	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3-N	Date and version identifier
Funding	4-P14	Sources and types of financial, material, and other support
Roles and responsibilities	5a-P15	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a-P3	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7-P4	Specific objectives or hypotheses
Trial design	8-P4	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9-P4	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10-P5	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a-P6	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12-P8	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13-P7	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14-P11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15-N	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a-P5	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a-P5	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a-P4	Plans for assessment and collection of outcome, baseline, 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
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19-P10	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a-P11	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a-P10	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22-N	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23-N	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24-P11	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25-N	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a-P12	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28-P14	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29-N	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30-N	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a-P14	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32-N	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33-N	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.