PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Sun, Guo-li; Lei, Li; Liu, Liwei; Liu, Jin; He, Yibo; Guo, Zhaodong; dai, xiaohua; He, Lihao; Chen, Shi-qun; Liang, Yan; Ye, Jianfeng; Hu, Yunzhao; Chen, Guoqin; Chen, Ji-yan; Liu, Yong

VERSION 1 – REVIEW

REVIEWER	Robert Byrne Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
REVIEW RETURNED	20-Aug-2019

GENERAL COMMENTS	In their manuscript Guoli Sun et al. present the study design and rationale for the WECHAT study. Overall, the study is innovative and addresses an unmet need for therapy adherence with the help of an applet and social media. The potential relevance of such studies is broad. People grow up with these technologies and become potentially a patient sometime in the future. Thus, the inclusion of digital media will play an even more important role in the future. I have the following comments: 1. The current ESC guidelines generally recommend 6 months (not 12 months) of DAPT in patients with stable CAD who underwent PCI or 12 months of DAPT in case of an ACS. The authors should clarify this. 2. The authors write: "… will be conducted in the Department of Cardiology of five hospitals. A total of 760 patients in 4 hospitals…" Please clarify. 3. The authors describe, that patients should take DAPT for at least 1 year after doctor's evaluation. How do the authors proceed with patients with an indication for a shorter DAPT, for example most of the patients with stable CAD or patients with a high bleeding risk? 4. What was the rationale for medical knowledge education messages and follow-up reminders in the control group and not just standard care? 5. How do the authors plan to measure the medication adherence? Or in other words: how do the authors plan to make sure the patient took the medication and not just punched a time clock? Are there any further objective measurements planned, e.g. pill counts or measurement of the platelet activity? 6. How do the authors ensure the patient's data safety and that the patients data are not used by a third party? 7. Are there any pre-specified subgroup analysis planned?

	8. Are there any technical requirements for the patients? Is a patient training for the applet planned? 9. How do the authors plan to proceed with emergency messages transmitted via social media platforms, especially outside of the regular business hours? 10. How do the authors plan to rule out selection bias? Patients with a low socioeconomic status possibly don't have a smart phone and on the other hand patients with a high socioeconomic status (who possibly use smart phones more often) are well known to have a higher compliance to medical therapies. 11. Please review the timelines for enrollment on page 10, which do not appear to be internally consistent (e.g. "2019/01/01-2020/12/31 Enrollment will be completed during the 4 months…"). 12. I had some difficult reproducing exactly the sample size calculation with nQuery Advisor. Using two-sided chi-squared testing and the assumptions detailed on page 15-16 I calculated that 406 patients per group were necessary without accounting for dropouts.

REVIEWER	Elvin Kedhi Isala Hartctr
REVIEW RETURNED	24-Aug-2019

GENERAL COMMENTS	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 This reviewer read with interest this manuscript. This is an interesting study. Please find attached my comments Comments: Strengths and limitations of this study section 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. It is not clear which these 4 drugs are. DAPT mention in the title leaves believe that the study focuses on 2 drugs (ASA, and P2Y12 inhibitors) Abstract section 1) Methods: Please structure the method section in short description study design, short description study population. Then describe endpoints followed by a short description statistic methods and power calculation. Add shortly between brackets what discontinuation definition is. 2) 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. This is not clear , please rephrase. Keywords:

	please consider: Mobile health, Drug Eluting Stents, Dual Antiplatelet Therapy, Randomized Controlled Trial Study Design. Please provide here a general description of the two arms Avoid giving information on patient number here, this will be done in the power calculation section. Data Collection: 1) Please provide information where the data will be stored. Is there a CRO involved? 2) Please provide information about confidentiality of the patient data made available to the company. If this the case does patient grant permission for this aspect too? Is this reflected in the patient information form? Study Population Please consider an to improve English language in this section (and through entire manuscript) This section does not read fluently. But we have enrolled 36 patients undergoing DES implantation for internal testing. Consider deleting this sentence and mention that a pilot phase in 36 patients has taken place… Study intervention Please move this entire section to follow after the section Study design. Please provide tables with Whechat platform messages used in both arms so the reader could understand how this was practically done. (eventually as supplement tables) Please provide more information about the number of researcher / patient contacts for each arm. It appears now that the researchers have monthly contact with patients in the intervention arm. This of course diminishes the impact of Whechat in this arm (if this is the case) It appears that the intervention arm reminders are directed also to medications beyond DAPT as well as they receive a more accurate AHT monitoring. Please explain. If this is the case, please reflect these interventions also in the tittle, Introduction as well as in power calculation which simply focuses on DAPT now. Definitions 1) It is not clear what the definition of discontinuation is for the purpose of this trial Is it 7, 15 or 30 days? 2) It seems not logical to count as a discontinuation a patient decision to swich to another P2Y12. This biases the study as these patients would not technically forget to take the drug

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. The current ESC guidelines generally recommend 6 months (not 12 months) of DAPT in patients with stable CAD who underwent PCI or 12 months of DAPT in case of an ACS. The authors should clarify this.

Response: Thank you for your suggestion. To clarify the duration of DAPT, we carefully reviewed the literature and redrafted our inclusion criteria. Patients with ACS can be enrolled as far as is possible. We will also use Precise-DAPT scores to evaluate the duration of DAPT for patients with stable CAD. Those who are recommended to undergo 12 months of DAPT can also be enrolled. The description has been revised in the manuscript's methods section (Paragraph 5, Page 5).

2. The authors write: "… will be conducted in the Department of Cardiology of five hospitals. A total of 760 patients in 4 hospitals…" Please clarify.

Response: Thank you for your comments. We apologize for our carelessness. The recruitment sites include 5 public hospitals in China. We have revised the two sentences in the methods section (Paragraph 2, Page 4) that discuss this point. We have also carefully checked the manuscript and corrected the errors accordingly.

3. The authors, describe that patients should take DAPT for at least 1 year after doctor's evaluation. How do the authors proceed with patients with an indication for a shorter DAPT, for example most of the patients with stable CAD or patients with a high bleeding risk?

Response: Thank you for your suggestion, and we have adjusted the inclusion and exclusion criteria accordingly. All patients will be evaluated at 6 months using Precise-DAPT scores.

We will exclude patients with an indication for a shorter DAPT, such as most patients with stable CAD or with high bleeding risk. We have revised statements on this qualification in the methods section (Paragraph 5, Page 5).

4. What was the rationale for medical knowledge education messages and follow-up reminders in the control group and not just standard care?

Response: Thank you for your sincere comment. From a methodological perspective, it is a priority to balance e-based support across the control and experimental arms of the trial to ensure that differences in nonspecific support and attention do not confound potential improvement in clinical outcomes. Therefore, controls will be supported with educational material that will include brief articles on heart health. Our design also refers to other research, such as the REACH study. We have also added the protocol from the REACH study for reference in the methods section (Paragraph 1, Page 10).

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.

5. How do the authors plan to measure medication adherence? Or in other words: how do the authors plan to make sure the patient took the medication and not just punched a time clock? Are there any further objective measurements planned, e.g. pill counts or measurement of the platelet activity?

Response: Thank you for your suggestion. To measure drug adherence more precisely, medication adherence will be evaluated by the proportion of days covered by pills (PDC). Patients will be defined as adherent if they report that they have taken their indicated medications on >80% of days. Since it's a generally accepted way in many countries and publications.

6. How do the authors ensure the patient's data safety and that the patients' data are not used by a third party?

Response: Thank you for your comments. We have added the statement 'Confidentiality agreements have been signed with third-party companies' to the methods section (Paragraph 2, Page 12). Third parties will not use relevant data for commercial purposes, and they are required to promise to protect patients' privacy. Data will not be stored in self-built storage equipment. Data access will require authorization. Data desensitization will also be applied.

7. Are there any pre-specified subgroup analysis planned?

Response: Thank you for your question. In the statistical analysis, the study will conduct subgroup analysis based on relevant patient baseline data, such as age, education level and socioeconomic status, using logistic regression models with the intervention group. We have revised the methods section to include this statement (Paragraph 1, Page 16).

8. Are there any technical requirements for the patients? Is a patient training for the applet planned?

Response: Thank you for your comments. Our applet is based on WeChat, which can be used on any smartphone. We did not have many technical requirements except that participants use WeChat and smartphones. We describe the requirements in our revised methods section (Paragraph 1, Page 6).

To make the enrolment process easier, we have developed training materials, such as a brochure and video, to introduce the applet to the patients and show them how to use it. They will also receive some face-to-face training when they are enrolled.

9. How do the authors plan to proceed with emergency messages transmitted via social media platforms, especially outside of the regular business hours?

Response: Thank you for your suggestion. During interactions on the social media platform, the applet will send a pop-up reminder to patients that urgent questions are not allowed. If there is an

emergency, the applet will remind the patient to go to the hospital for immediate treatment/first aid. Besides, the patients will receive detailed training on the applet's functions and notifications. This information has been added to the interactive responses section (Paragraph 2, Page 9).

10. How do the authors plan to rule out selection bias? Patients with a low socioeconomic status possibly don't have a smart phone and on the other hand patients with a high socioeconomic status (who possibly use smart phones more often) are well known to have a higher compliance to medical therapies.

Response: Thank you for your comments. We agree with your concern. Studies on social media face numerous challenges and limitations, such as low enrolment rate and selection bias. However, the smartphone penetration rate in China is as high as 83%, according to Google's consumer barometer report in 2017.

Although selection bias is unavoidable, we chose to use the design of a randomised, double-blind study to reduce it. We will also conduct a subgroup analysis based on the patients' socioeconomic status and mobile usage to reduce selection bias.

The report link:

https://www.consumerbarometer.com/en/trending/?countryCode=CN&category=TRN-NOFILTER-ALL

11. Please review the timelines for enrollment on page 10, which do not appear to be internally consistent (e.g. "2019/01/01-2020/12/31 Enrollment will be completed during the 4 months…").

Response: Thank you for your reminder. We have corrected the timeline. We have corrected the statement to say '2019/01/01 – 2020/12/31 Enrolment is to be completed over 24 months' in the timeline section (Paragraph 2, Page 10).

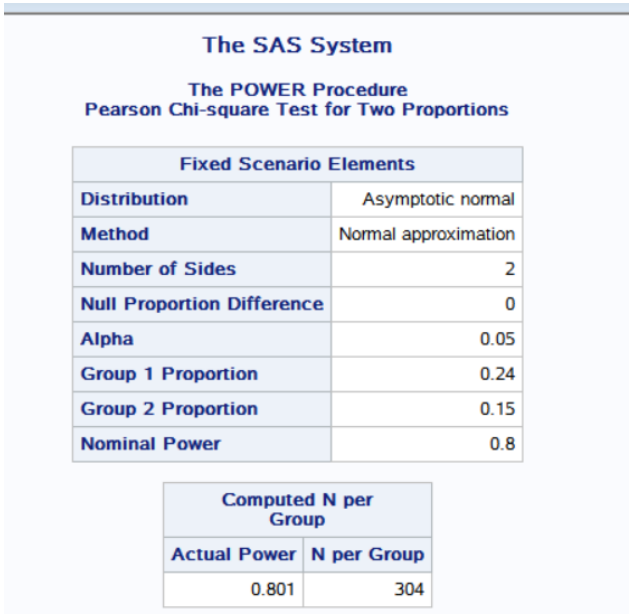
12. I had some difficult reproducing exactly the sample size calculation with nQuery Advisor. Using two-sided chi-squared testing and the assumptions detailed on page 15-16 I calculated that 406 patients per group were necessary without accounting for dropouts.

Response：Thank you for your comments. We confirmed the method for the sample size calculation with a statistician. The power is 80% and we use SAS 9.4 to calculate it ultimately, instead of nQuery Advisor. The description has been revised in the statistical analysis section (Paragraph 1, Page 15). The code in SAS and the result are as follows(Figure 1). We have also verify the sample size through PASS and it is 760(Figure 2).

The code in SAS:

proc power;

```
twosamplefreq test=pchi

grouppproportions=(0.24 0.15)

nullproportiondiff=0

npergroup=.

sides=2

alpha=0.05

power=0.80;

run;
```



The SAS System

The POWER Procedure
Pearson Chi-square Test for Two Proportions

Fixed Scenario Elements	
Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	2
Null Proportion Difference	0
Alpha	0.05
Group 1 Proportion	0.24
Group 2 Proportion	0.15
Nominal Power	0.8

Computed N per Group	
Actual Power	N per Group
0.801	304

Figure 1.The sample size in PASS

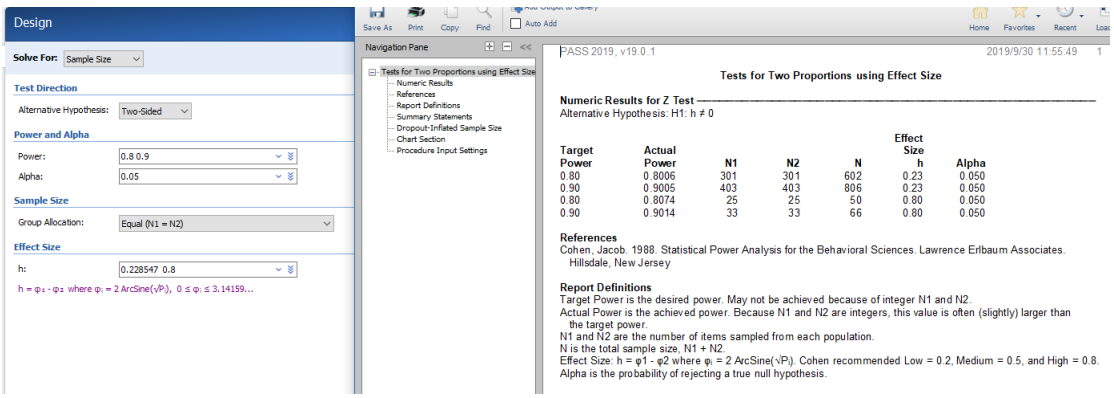


Figure 2 .The sample size in PASS

Reviewer: 2
Reviewer Name: Elvin Kedhi
Institution and Country: Sint-Jan Hospital
Brugges Belgium
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below
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 randomised controlled study

This reviewer read with interest this manuscript. This is an interesting study. Please find attached my comments
Response: Thank you again for your comments and valuable suggestions to improve the quality of our manuscript.

Comments:
1.Strengths and limitations of this study section
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.
It is not clear which these 4 drugs are. DAPT mention in the title leaves believe that the study focuses on 2 drugs (ASA, and P2Y12 inhibitors)
Response: Thanks for your correction. We apologise for our carelessness. We focus on DAPT since they are crucial to the long-term outcomes. The mistake has been revised in our resubmitted manuscript (Paragraph 3, Page 2).

2. Abstract section
1) Methods: Please structure the method section in short description study design, short description study population. Then describe endpoints followed by a short description of statistic methods and power calculation. Add shortly between brackets what discontinuation definition is.
Response: Thanks for your comments. According to your suggestion, we have revised the methods section. Study design, population, endpoints, statistical methods, and definitions have been included in the revised manuscript. (Paragraph 3, Page 2)

2) 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. This is not clear ,

please rephrase.

Response: Thank you for your sincere comments. We have revised the statement to say ‘The study will first evaluate the effects of interactive responses and medication reminders via social media on improving compliance with DAPT’ in the abstract section of the revised manuscript (Paragraph 3, Page 3).

3. Keywords:

please consider: Mobile health, Drug Eluting Stents, Dual Antiplatelet Therapy, Randomised Controlled Trial

Response: Thank you for your sincere suggestions. We have revised the keywords for the revised manuscript according to your suggestion(Paragraph 1, Page 4).

4. Study Design.

Please provide here a general description of the two arms

Avoid giving information on patient number here, this will be done in the power calculation section.

Response: Thank you for your sincere suggestions. We have deleted the sample size in the study design section (Paragraph 2, Page 5). A description of the two groups has been added to the design section (Paragraph 2, Page 5).

5. Data Collection:

1) Please provide information where the data will be stored. Is there a CRO involved?

Response: Thank you for your sincere comments. There is a third party(CRO) involved, and data management is managed by a secure clinical trial data management team.

2) Please provide information about confidentiality of the patient data made available to the company. If this the case does patient grant permission for this aspect too? Is this reflected in the patient information form?

Response: Thank you for your comments. We agree that the possibility of breaching confidentiality should not be underestimated. We have signed a confidentiality agreement with information management to ensure patients’ privacy and confidentiality. Authorisation is required for company personnel to access core data, such as demographic information, medical history and examinations. They cannot reserve or transmit the data without permission.

The relevant information on privacy and confidentiality will be reflected in the informed consent form. We have added the description in the Data and Safety Monitoring Board section(Paragraph 2, Page 5).

6. Study Population

(1). Please consider an to improve English language in this section (and through the entire manuscript) This section does not read fluently.

Response: Thanks for your suggestion. The manuscript has been sent to a professional and native speaker, and we have tried our best to polish the language used in the revised manuscript.

(2).But we have enrolled 36 patients undergoing DES implantation for internal testing.
Consider deleting this sentence and mention that a pilot phase in 36 patients has taken place…

Response: Thank you for your sincere suggestions. In the timeline section, we deleted this sentence and explained that a pilot phase had taken place with 36 patients for design optimization (Paragraph 3, Page 10).

7. Study intervention

(1) Please move this entire section to follow after the section Study design.

Response: Thanks for your nice suggestions. The entire section has been removed.

(2) Please provide tables with Wechat platform messages used in both arms so the reader could understand how this was practically done. (eventually as supplement tables)

Response: Thank you for your comments. The message tables help to explain our study design and practice more clearly. The messages are shown below. It will be a supplementary table.

Supplement table1. Examples of messages text ms s the intervention

group

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.	*Personalized reminder* *-For patients with diabetes* -It is recommended that you check your blood glucose regularly.

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.	-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 all your medicine 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.

(3).Please provide more information about the number of researcher / patient contacts for each arm. It appears now that the researchers have monthly contact with patients in the intervention arm. This of course diminishes the impact of Wechat in this arm (if this is the case)

Response: thank you very much for your sincere suggestions. In fact, three senior researchers and 3 trained researchers will guide the trained research assistants on how to communicate with the patients in the intervention group. WeChat may provide other platforms to communicate with patients, like Facebook or Twitter. It is extremely important to improve users' adherence. However, frequent contact will also increase the workload of doctors in clinical practice. So, we have designed an auto-response function. After reviewing the literature and analyzing our pilot study, we found that once a month to be a good time interval.

(4).It appears that the intervention arm reminders are directed also to medications beyond DAPT as well as receive a more accurate AHT monitoring. Please explain. If this is the case, please reflect these interventions also in the tittle, Introduction as well as in power calculation which simply focuses on DAPT now.

Response: Thank you for your suggestions. I assume that you mean the intervention will also affect other important factors. The study aims to explore the effect of social media on DAPT adherence. Bias is inevitable. So, the intervention will focus on adherence to DAPT rather than AHT monitoring. The clarification has been revised in the intervention group section (Paragraph 1, Page 8).

8. Definitions
1) It is not clear what the definition of discontinuation is for the purpose of this trial
Is it 7, 15, or 30 days?

Response: Thank you for your sincere comments. It is difficult to define discontinuation, so we consulted many references. In this study, discontinuation is defined as a cessation of any antiplatelet treatment within 1 year of DES implantation. The discontinuation duration is to be further segmented into periods after the index disruption event, i.e., brief (1–7 days), temporary (8–30 days) and permanent (>30 days) based on follow-ups and records of medication adherence on social media or the prescription. The definition is the same as that in the PARIS study (as following).

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.

2) It seems not logical to count as a discontinuation a patient decision to switch to another P2Y12. This biases the study as these patients would not technically forget to take the drug
Response: Thank you for your comments. Switching drugs is allowed in the study. Changing DAPT medication between ticagrelor and clopidogrel under doctors' recommendations will not be identified as dual antiplatelet drug discontinuation.

We will only record whether patients have stopped DAPT.

VERSION 2 – REVIEW

REVIEWER	Prof. Robert Byrne Deutsches Herzzentrum München Klinik für Herz- und Kreislauferkrankungen
REVIEW RETURNED	15-Nov-2019

GENERAL COMMENTS	The responses to the issues raised is generally satisfactory. I have no further comments.