Impact of a pharmaceutical care service for patients with rheumatoid arthritis using a customised mobile device (the PROUD trial): study protocol for a randomised controlled trial

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ABSTRACT

Introduction Rheumatoid arthritis (RA) generally requires lifelong treatment; however, its medication complexity might affect non-adherence. Pharmacist-led telehealth services were as effective as face-to-face services and reduced potential side effects in outpatients with chronic diseases. This study aims to analyse the effect of a telepharmacy service with a customised mobile device in comparison with the usual pharmacist service on the humanistic and clinical outcomes in patients with RA.

Methods and analysis The study is designed as a prospective, randomised, open-label, and controlled trial to compare the humanistic and clinical outcomes of the pharmaceutical care service with monthly telecommunications and a customised mobile application (telepharmacy care group) against the usual service by community pharmacists (usual care group) in 256 patients with RA and prescribed at least one of the disease-modifying antirheumatic drugs. Participants will be recruited from a tertiary hospital in Republic of Korea with written informed consent. The primary outcome will be the changes in health-related quality of life as measured by the Korean version of the EuroQoL's five-dimensional questionnaire at 6 months compared with baseline. The secondary outcomes will be the changes in the following: scores of the Korean version of the Compliance Questionnaire-Rheumatology and medication knowledge at 3 and 6 months compared with baseline; scores of the Korean version of the Pharmacy Service Questionnaire at 6 months compared with baseline; clinical parameters such as erythrocyte sedimentation rate, C reactive protein level, and pain score at 3 and 6 months compared with baseline; frequency of acute care utilisation over 6 months. Analysis will be carried out with intent-to-treat and per-protocol principles.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This study will evaluate the effect of a telepharmacy service in comparison with the usual service provided by community pharmacists for patients with rheumatoid arthritis (RA) in the setting of a prospective, randomised, open-label and controlled trial design.

For the participants in the intervention group, the clinical pharmacists will review the laboratory results, medication and disease history of the participants in the electronic medical records, and then call the participants every month for medication counselling.

The MediRA app, a customised mobile application developed for this study, will be installed on the smartphone of the participants in the intervention group to provide the customised information about the drugs that they will be taking and set an alarm for non-daily medications.

The primary outcome is the changes in health-related quality of life as measured by the EuroQoL's five-dimensional questionnaire at 6 months compared with baseline.

This study will be conducted in a single centre in one Asian country, and thus, the findings may not be generalisable to all locales.

INTRODUCTION

Rheumatoid arthritis (RA), characterised by a persistent inflammatory response in the synovial membrane of joints, generally requires lifelong treatment to prevent joint damage and preserve bone density.1 Disease-modifying antirheumatic drugs (DMARDs) including conventional or biological DMARDs and Janus kinase (JAK) inhibitors, as well as symptomatic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, are mainly used for the lifetime management of RA.1 5 It has been reported that 99.7% of the patients with RA...
received outpatient care, of whom 80.8% were in their 50s or older in Korea, which might have affected medication non-adherence and therapeutic failure. Furthermore, intentional and unintentional non-adherence with RA drugs accounted for 24.2% and 31.8%, respectively, which might be due to the medication complexity or low confidence in pharmacotherapy. Therefore, standardised and personalised pharmaceutical services delivered by pharmacists are necessary to meet the patients’ needs for medication counselling and to improve adherence and therapeutic outcomes.

Several studies have been conducted to evaluate the effectiveness of pharmacist services on the improvement of satisfaction and medication compliance in European patients with RA. Mary et al. demonstrated that a continuous pharmacist service sending mobile phone text messages every week for 6 months had a positive effect on the improvement of treatment adherence compared with pharmacist-led medication counselling in patients taking methotrexate for RA. However, there have been few randomised controlled trials to assess the impact of systematic pharmaceutical care services on quality of life, and clinical outcomes prospectively considering the characteristics of patients with RA.

In the era of the fourth industrial revolution with information and communication technologies (ICTs) at its core, telepharmacy services appear to be an innovative way to deliver pharmacist care services through the use of telecommunications. The COVID-19 pandemic crisis has affected patients currently residing at a distance from a remotely located hospital, pharmacy or healthcare centre, or being requested to be in quarantine, which has increased the need for telepharmacy. It has been reported that pharmacist-led telehealth services using ICT were at least as effective as face-to-face services, and reduced potential side effects and hospital admissions in outpatient populations with chronic diseases especially where usual care could not be provided. Therefore, this study aims to analyse the effect of a telepharmacy service involving a customised mobile device in comparison with the usual pharmacist service on the humanistic and clinical outcomes of patients with RA (the PROUD trial).

## METHODS AND ANALYSIS

### Trial design

The PROUD Study is designed as a prospective, randomised, open-label, controlled trial to compare the humanistic and clinical outcomes of the pharmaceutical care service. It involves the usage of customised mobile device for 256 participants diagnosed with RA with the usual service by community pharmacists. Patients will be recruited from a tertiary hospital, the Daegu Catholic University Medical Center (DCMC) in Daegu, Republic of Korea. The ICT-integrated pharmaceutical care service will be provided through monthly telephone calls and irregular text messages by clinical pharmacists in the DCMC, and supplemented with a smartphone application developed for participants with RA (named MediRA). Due to the characteristics of this service intervention study, group allocation will not be

### Figure 1

PROUD Study design. CRP, C reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; JAK, Janus kinase; K-CQR, Korean version of the Compliance Questionnaire-Rheumatology; K-EQ-5D, Korean version of the EuroQoL’s five-dimensional questionnaire; K-PSQ, Korean version of the Pharmacy Service Questionnaire; VAS, Visual Analogue Scale.

### Figure 2

Flow diagram of the study design.
concealed from the investigators and participants during the experiments. The study will follow the Standard Protocol Items Recommendations for Interventional Trials and the Consolidated Standards of Reporting Trials.15 16

Participants and setting
The inclusion criteria of our study are that the participants: (1) be at least 18 years old; (2) be diagnosed with RA by a rheumatologist at the DCMC and prescribed at least one of the following DMARDs: conventional synthetic DMARDs (hydroxychloroquine, methotrexate, sulfasalazine, bucillamine or leflunomide), biological DMARDs administered subcutaneously (etanercept, adalimumab, golimumab, abatacept or tocilizumab) and JAK inhibitors (tofacitinib, baricitinib or upadacitinib); (3) taking DMARDs, steroids or analgesics for the first time for the management of RA or changed prescription of DMARDs at the time of randomisation; and (4) using a mobile device such as a smartphone. Patients will be excluded from the study if they (1) are unable to respond to surveys or interviews due to deterioration in cognitive abilities or other similar conditions; (2) have severe systemic or malignant diseases; (3) fail or disagree to install a mobile application called MediRA which is a customised medication guide for patients with RA; or (4) are deemed inappropriate to provide regular telepharmacy service using telecommunications due to hearing impairment. Participants will attend a study explanation session and be provided with a written consent form to participate before enrolling in the study (online supplemental appendix 1).

Participants’ recruitment
The participants will be recruited from the outpatient clinics and wards of the Rheumatology Department at the DCMC via posted flyers and word of mouth by physicians or research nurses. Recruitment posters will be provided in outpatient clinics and wards, and these will include general information about the research and purpose for the participants. The principal researchers in this study will not rule out patients who are likely to participate in this study based solely on age or socioeconomic status. The patients will be enrolled after being provided with sufficient information by the researchers and obtaining written informed consent. The participants will be asked to fill out the consent form by themselves to minimise the possibility of forced or unfair effects. In the process of obtaining consent, the researchers will explain this study in Korean using terms that the participants could understand. The first patient was enrolled on 30 August 2021. It is estimated that this study will be completed by 31 December 2023.

Randomisation
An independent trial statistician generated the randomisation sequence using a computer-generated list called the Sealed Envelope (https://www.sealedenvelope.com/) with a block size of six. After signed consent is obtained from eligible participants, the site investigators in the DCMC will screen the participants for recruitment and contact a trial coordinator to receive the randomisation sequence, ensuring concealment of allocation. The participants will be randomly assigned to either of the two arms with a 1:1 allocation ratio in the order of consent. The randomisation sequence has two parallel arms, a control or usual care (UC) group and an intervention or telepharmacy care (TC) group. Participants will be informed of their assigned group within 7 days after randomisation by the clinical pharmacists in the DCMC.

Interventions
The participants randomised to the TC group will receive the ICT-integrated pharmaceutical care service by the clinical pharmacists at the DCMC in addition to the existing pharmacist services at community pharmacies. For the participants in the TC group, the clinical pharmacists will review the laboratory results, medication and disease history of the participants in the electronic medical records (EMRs), and the participants will be called every month for medication counselling. The monthly counselling will be conducted according to a standardised guideline of telepharmacy services for patients diagnosed with RA which includes the following: (1) medication review to gather the patients’ entire medication information, including prescription drugs from other hospitals, over-the-counter drugs and dietary supplements; and (2) medication evaluation and management to discuss the drug-related problems (DRPs), such as adverse reactions (signs and symptoms, date of the occurrence and more), drug interactions, duplicated medications, non-adherence and acute care utilisation such as emergency rooms or hospitalisation in the past month.17 The causal relationships of the adverse reactions with the medicines will be assessed based on the Naranjo algorithm, and the following adverse reactions will be considered as serious adverse events: death, a life-threatening event, hospitalisation (either initial or extended), disability or permanent damage, congenital anomaly or birth defect, and other significant medical events.18 19 The non-adherence will be evaluated by conducting a survey with the validated Korean version of the Compliance Questionnaire-Rheumatology (K-CQR) and asking the participants about the number of drugs for the management of RA they had.20 The severity of the identified DRPs will be assessed using the Severity Categorization for Pharmaceutical Evaluation criteria, among which information with a severity level of IV or higher is provided to the physician.21 The pharmacists will be provided with a manual for the telepharmacy services and a case report form (CRF). After the monthly telepharmacy service, the participants will be notified of the next scheduled service, and the following information will be recorded on the CRF by the pharmacist: the initials of the pharmacist’s name, date and time of the service, and the participant’s queries and answers.
We developed the MediRA app, a customised mobile application for patients with RA to provide the medication information in a user-friendly way and to improve their compliance. The app will be installed for the participants in the TC group on their smartphones with the operating system of Google’s Android or Apple’s iOS with the help of the installation guide and the coordinator (figure 3). The app contains the following medication information for the drugs prescribed at the DCMC for the treatment of RA (table 1): generic name, ingredient, picture of the drug, ‘what is this drug used for?’, ‘how much of this drug do I take?’, ‘when and how do I take this drug?’, ‘what do I do if I miss a

**Table 1** Drug list in the MediRA app

| Category                  | Ingredient              | Formulation       | Dosage                  |
|---------------------------|-------------------------|-------------------|-------------------------|
| Conventional synthetic DMARDs | Methotrexate            | Tablet            | 2.5 mg/tablet           |
|                           | Leflunomide             | Tablet            | 10 mg/tablet            |
|                           | Sulfasalazine           | Tablet            | 500 mg/tablet           |
|                           | Hydroxychloroquine sulfate | Tablet          | 100 mg/tablet; 150 mg/tablet; 200 mg/tablet; 300 mg/tablet |
|                           | Bucillamine             | Tablet            | 100 mg/tablet           |
|                           | Azathioprine            | Tablet            | 25 mg/tablet; 50 mg/tablet |
|                           | Cyclophosphamide        | Tablet            | 50 mg/tablet            |
|                           | Microemulsion ciclosporin | Capsule          | 25 mg/cap               |
|                           | Tacrolimus hydrate      | Capsule           | 0.5 mg/cap; 1 mg/cap    |
| Biological DMARDs         | Etanercept              | Vial              | 25 mg/vial; 50 mg/mL    |
|                           | Pen injector            | Prefilled syringe | 50 mg/mL                |
|                           | Adalimumab              | Pen injector      | 40 mg/0.4 mL            |
|                           | Prefilled syringe       |                   | 40 mg/0.4 mL            |
|                           | Golimumab               | Prefilled syringe | 50 mg/0.5 mL; 100 mg/mL |
|                           | Abatacept               | Prefilled syringe | 125.875 mg/mL           |
|                           | Tocilizumab             | Pen injector      | 162 mg/0.9 mL           |
| JAK inhibitors            | Tofacitinib             | Tablet            | 5 mg/tablet             |
|                           | Baricitinib             | Tablet            | 2 mg/tablet; 4 mg/tablet |
|                           | Upadacitinib            | Extended-release tablet | 15 mg/tablet          |
| NSAIDs                    | Nabumetone              | Tablet            | 500 mg/tablet           |
|                           | Aceclofenac             | Tablet            | 100 mg/tablet           |
|                           | Meloxicam               | Capsule           | 7.5 mg/cap; 15 mg/cap   |
|                           | Celecoxib               | Capsule           | 100 mg/cap; 200 mg/cap  |
| Analgesics                | Acetaminophen, tramadol | Tablet            | 162.5 mg, 18.75 mg/tablet; 325 mg, 37.5 mg/tablet |
|                           |                         | Extended-release tablet | 325 mg, 37.5 mg/tablet; 650 mg, 75 mg/tablet |
|                           | Glucocorticoids         | Prednisolone      | 5 mg/tablet             |
|                           | Methylprednisolone      | Tablet            | 4 mg/tablet             |
|                           | Dexamethasone           | Tablet            | 0.5 mg/tablet           |
|                           | Triamcinolone           | Tablet            | 1 mg/tablet; 2 mg/tablet; 4 mg/tablet |
|                           | Deflazacort micronised  | Tablet            | 6 mg/tablet             |

DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs.
dose?’, ‘what are the side effects of this drug?’, ‘what can affect the efficacy or safety of this drug?’ and ‘what should I be aware of when taking this drug?’ For the self-administered injectable drugs such as etanercept, adalimumab, golimumab, abatacept and tocilizumab, we have provided a video in the app explaining how to administer them.22–25

Using a user interface of https://admin.medira.co.kr/, researchers can provide customised information about the drugs that participants in the TC group will be taking, and set an alarm for non-daily medications (that is, methotrexate, biological DMARDs) in the app. As shown in figure 3, participants can log in to the app with the hospital registration number as an online identification, and check the list and dosing frequency of drugs that the participant should take on the day, as well as the above drug-specific information. In addition, the participant can get the information through text or voice whenever they need it and can send a text message or call the clinical pharmacists using the app if they have any questions or notice any side effects.

Participants in the control group will receive usual care from local community pharmacists without the implementation of a telepharmacy care model. Usual care consists mainly of dispensing prescribed drugs and providing basic education on the safety and appropriate use of the medicines. The community pharmacies visited by the participants will not be informed about the enrolment of the participants in this study.

Outcome measures

Primary outcome measurements

The primary outcome of this study will be the changes in health-related quality of life (HRQoL) as measured by the validated Korean version of the EuroQol’s five-dimensional questionnaire (K-EQ-5D) at 6 months compared with baseline.26 27 HRQoL in participants with progressive chronic diseases has become a major patient-reported outcome indicator in both research and clinical practice.28 The EQ-5D is a generic HRQoL assessment tool, which has been reported to be valuable for assessing HRQoL especially in Asian patients diagnosed with RA.29 30 It can be obtained by filling out the registration form through https://registration.euroqol.org/ and we have received permission for its use from the EuroQol Research Foundation.31 The questionnaire consists of two parts: a descriptive system (EQ-5D-5L) and a Visual Analogue Scale (EQ-5D-VAS). The EQ-5D-5L describes health status in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with five levels of responses. The EQ-5D-VAS records the patient’s self-assessed health in general with a 100 mm score, where 0 indicates the worst imaginable health state and 100 reflects the best.31 32 We applied a Korean translation of the EQ-5D that was validated for cultural authenticity.32

Secondary outcome measurements

Secondary outcomes will be as follows: (1) changes in scores of K-CQR at 3 and 6 months compared with baseline measurements; (2) changes in medication knowledge scores at 3 and 6 months compared with baseline; (3) changes in validated Korean version of the Pharmacy Service Questionnaire (K-PSQ) scores at 6 months compared with baseline; (4) changes in clinical parameters such as erythrocyte sedimentation rate (ESR) level, C reactive protein (CRP) level, pain score as measured by a 0–10 Numerical Rating Scale (NRS), and number of joint involvements at 3 and 6 months compared with baseline; and (5) frequency of acute care utilisation over 6 months.20 33

Compliance with medication therapy is important to achieve the desired therapeutic outcome for the management of RA.6 The CQR is a rheumatology-specific instrument that measures patient compliance with antirheumatic drug regimens and identifies factors for suboptimal patient compliance with 19 items.34 The participants will complete the questionnaire in their own environment at baseline, and at 3 and 6 months using the validated K-CQR.20 Medication knowledge and attitude of the participants will be evaluated at baseline, and at 3 and 6 months through administration of a modified brief medication questionnaire.35 Kim et al developed and validated a modified K-PSQ for the quality assessment of community pharmacy services. We will use this questionnaire to assess patient satisfaction regarding the pharmaceutical care services provided by the clinical pharmacists or the existing community pharmacies at baseline and at 6 months.33 The clinical parameters (ESR and CRP levels, pain score and number of joint involvements) will be measured through chart review at baseline, and at 3 and 6 months by the clinical pharmacists. In case of missing information in the pain score, the participants will be asked to rate their average pain over the past 24 hours on the NRS.

Utilisation data of the MediRA app will be collected by using the assessing number and assess time of the app for each participant in the TC group. In addition, satisfaction with the mobile app will be evaluated using a 5-point Likert scale.

Data collection and management

As shown in table 2, all outcomes will be collected at baseline and at 6 months, since the intervention for the participants in the TC group will be implemented for 6 months. Some outcomes such as K-CQR, medication knowledge and clinical parameters will be additionally collected at 3 months to evaluate the changes of each outcome over time. Data on baseline characteristics such as age, sex, date of first diagnosis of RA, duration of DMARDs, all medication profiles including newly prescribed drugs at the time of randomisation, over-the-counter drugs and dietary supplements, comorbidities (such as diabetes, high blood pressure, dyslipidaemia, heart disease, lung disease, kidney disease, ophthalmic disease, osteoporosis, anaemia, depression, thyroid disease), and family history will be collected before randomisation through chart review and participant interviews. The medications are classified as follows: conventional synthetic DMARDs, biological...
DMARDs, JAK inhibitors, NSAIDs, glucocorticoids, dietary supplements and others. In addition, information on the ingredients, generic name, dosage, administration and duration of administration of the medications will be collected. Vital signs (blood pressure and heart rate) and laboratory results related to dosage or adverse drug reactions (complete blood count including white cell count, absolute neutrophil count, haemoglobin level and platelet count; renal and hepatic function tests, such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, serum creatinine, blood urea nitrogen and creatinine clearance; fasting glucose; and total cholesterol level) or disease activity (ESR, CRP or NRS) will be collected by EMR review.

The humanistic outcomes such as K-EQ-5D, K-PSQ, K-CQR and medication knowledge will be recorded using an online survey software, SurveyMonkey, in both groups to evaluate the influences of the intervention on patients’ daily function, satisfaction and well-being.\textsuperscript{36,37} The participants in the TC group will be alerted to complete the questionnaire using the MediRA app to which the questionnaire is linked, and the participants in the UC group will receive a text message with the survey link information at fixed points in time. If the participants face difficulties taking an online survey, a written form will be provided to the participants by mail.

Any source data and questionnaires completed by the app or on paper will be stored in a space secured with a password to protect the personal information of the participants. Only the investigators of this study will have access to the study data. Information recorded in the CRF will be entered into a spreadsheet encrypted with a password by at least two study coordinators, and the data will be compared for quality control. The investigators will not attempt any access to information that could potentially violate the patient’s personal information.

Unnecessary personal identifiers will be removed when collecting data. Although personal information (such as contact number of the participants, prescription drugs and more) will be collected during the process of using the mobile applications, no collected information will reveal the identity of the participants. Mobile device information

| Time point | Enrolment | Allocation | Post-allocation |
|------------|-----------|------------|-----------------|
| Study week | −t\textsubscript{i} | t\textsubscript{0} | 4±1 | 8±1 | 12±1 | 16±1 | 20±1 | 24±1 |

Enrolment
- Eligibility screen X
- Informed consent X

Allocation X

Interventions
- Telepharmacy care X\textsuperscript{*}  X  X  X  X  X  X  X
- Usual care

Assessments
- Demographic information X
- K-EQ-5D X
- K-PSQ X
- K-CQR X
- Medication knowledge X
- CRP X
- ESR X
- VAS X
- Joint involvement X
- ER visits/hospitalisation
- AEs
- Mobile application utilisation X  X  X  X  X  X  X  X
- Mobile application satisfaction X

*Within a week after randomisation.

AEs, adverse events; CRP, C reactive protein; ER, emergency room; ESR, erythrocyte sedimentation rate; K-CQR, Korean version of the compliance questionnaire-rheumatology; K-EQ-5D, Korean version of the EuroQoL’s five-dimensional questionnaire; K-PSQ, Korean version of the Pharmacy Service Questionnaire; SPIRIT, Standard protocol items recommendations for interventional trials; VAS, Visual analogue scale.
Sample size
We estimated that an overall sample size of 233 participants would provide the study with a power of at least 80% to show a 5.1-point difference in EQ-5D-VAS level in an intervention group of pharmacists’ services compared with the control group, with an SD of 13.9 at a two-sided alpha level of 0.05. Assuming the dropout rate to be 10%, our target enrolment will be approximately 256 participants (128 participant per group).

Consideration of safety for the participants
Considering the objective of this study, any particular risk to the study participants is not expected. The participants may be withdrawn from the study at the discretion of the investigators for the following reasons: loss to follow-up, inappropriateness of the study participation based on the judgement of the investigators (such as cognitive impairment) or significant non-compliance with the study protocol. Participants will be informed that they could withdraw their participation voluntarily at any time and that even if the study is discontinued, the pharmacist services will be continuously provided as before, with no disadvantages to the discontinuation of the study.

Statistical analysis
Intent-to-treat (ITT) and per-protocol analyses will be conducted for all outcomes in all participants recruited prospectively, and for participants who would complete the study according to the protocol, respectively. All protocol deviations or violations will be included in the ITT analysis. Demographic data will be analysed by an intergroup comparison of the information collected at the time of randomisation. The changes in each primary and secondary outcome from baseline to 3 or 6 months in each group will be compared using the Wilcoxon signed-rank test. Data will be shown as numbers and percentages for categorical variables, means and SDs for continuous parametric data, and medians and IQR for non-parametric variables. Fisher’s exact and X² tests will be used to compare categorical data and unpaired t-test and Mann-Whitney test will be used to compare continuous data. The Spearman’s rank correlation coefficients will be used to identify bivariate relationships between HRQoL at baseline and at the 6-month follow-up. Correlation coefficients higher than 0.5 will be interpreted as showing a correlation, whereas those lower than 0.5 as showing little relationship. Multiple imputation will be used to handle missing outcome data. A subgroup analysis of participants with and without a first diagnosis of RA will be performed. Statistical significance will be set at a two-sided p<0.05, and data analysis and computation will be conducted using IBM SPSS Statistics for Windows, V.26 (IBM Corp) or SAS V.9.4 (SAS Institute). The research statistician, who will be blind to the study groups, will conduct the analysis.

Patient and public involvement
Patients and the public were not and will not be involved in the design, conduct or reporting of the study. During the study, participants will be assessed for 6 months of the study period, but they will not be able to access their CRF. The participants in the intervention group can check the medication information tailored to each individual provided through mobile apps. There are no plans to disseminate the results to the participants.

ETHICS AND DISSEMINATION
We will comply with the revised Helsinki Declaration at the 64th General Assembly of the World Congress in 2013 and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice guidelines for the planning and conducting this study. This trial was approved by the Institutional Review Board (IRB) of the DCMC (IRB no. CR-21-082-L, 14 July 2021) with a protocol version 4.0 (1 April 2021), and registered on the Clinical Research Information Service, Korea Disease Control and Prevention Agency (registration no. KCT0006508, 27 August 2021). All protocol amendments will be subjected to the IRB for approval and communicated with all investigators. The results of this study will be submitted for publication to peer-reviewed journals and presented at national and international conferences.

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Contributors
J-EP, J-EL, J-WK and Y-KS designed the trial. Y-KS obtained funding for the trial. J-EP, J-WK and Y-KS drafted the manuscript. B-KM, HL, S-HP, S-KK and J-YC provided critical revision of the manuscript. All authors discussed and helped to improve the protocol, and read and approved the final manuscript.
