BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061917
Article Type:	Protocol
Date Submitted by the Author:	10-Feb-2022
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Keywords:	RHEUMATOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS

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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Word count 3,682

ABSTRACT

Introduction This study aims to analyse the effect of an integrated tele-pharmacy service with a customised mobile device compared to usual pharmacist service on the humanistic and clinical outcomes in patients with rheumatoid arthritis (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 integrated pharmaceutical care service with a monthly telecommunications and a customised mobile application (tele-pharmacy care (TC) group) against the usual service by community pharmacists (usual care (UC) group) in 282 patients with RA and prescribed at least one of the disease-modifying antirheumatic drugs. The primary outcome will be the changes in health-related quality of life as measured by the Korean version of the EuroQoL five-dimensional questionnaire at 6 months compared to baseline. Secondary outcomes will be the changes of the followings: scores of the Korean version of the compliance questionnaire-rheumatology and medication knowledge/attitude at 3 and 6 months compared to baseline measurements; scores of the Korean version of the pharmacy service questionnaire at 6 months compared to baseline; clinical parameters such as erythrocyte sedimentation rate, C-reactive protein level, and pain score at 3 and 6 months compared to baseline; frequency of acute care utilisation over 6 months. Analysis will be carried out with intent-to-treat and per-protocol principles.

Ethics and dissemination The study protocol was reviewed and approved by the institutional review board of Daegu Catholic University Medical Center. The study findings will be published in peer-reviewed journals.

Trial registration number KCT0006508

Keywords Rheumatoid arthritis, tele-pharmacy service, personalised mobile applications, humanistic outcomes, clinical outcomes

Article Summary

- This is a pioneering study for evaluating the effect of an integrated tele-pharmacy service with a customised mobile device for patients with rheumatoid arthritis (RA) on humanistic and clinical outcomes using a prospective, randomised, open-label, and controlled trial design (the PROUD trial).
- The study will compare the integrated pharmaceutical care service involving a customised mobile device with the usual service provided by community pharmacists in patients with RA.
- The intervention group will be provided an integrated pharmaceutical care service by the clinical pharmacists based on monthly telecommunication Tele-pharmacy services, which provide medication history management services as well as the MediRA app, a customised mobile application developed for this study.
- The results of this trial will be most applicable for pharmaceutical care services by clinical pharmacists in tertiary hospitals since there is no participation of pharmacists from community pharmacies in this study.
- Further global multi-centre studies will be necessary because this study will be conducted in a single centre in only one Asian country, and 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. 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, 2] It has been reported that 99.7% of the patients with RA have received outpatient care, and 80.8% of them were in their 50s and older in Korea, which might have affected medication nonadherence and therapeutic failure in patients with RA.[3, 4] Moreover, intentional and unintentional nonadherence with RA drugs accounted for 24.2% and 31.8%, respectively, which might be due to the medication complexity or low confidence in pharmacotherapy.[4] Therefore, standardised and personalised pharmaceutical services delivered by pharmacists are necessary to meet the patients' needs for medication counselling and improve adherence and therapeutic outcomes.[5, 6]

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.[7, 8] 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 to pharmacist-led medication counselling in patients taking methotrexate for RA.[8] 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 (ICT) as the core, tele-pharmacy services appears to be an innovative way to deliver pharmacist care services through the use of telecommunications.[9, 10] The current

Coronavirus Disease 2019 (COVID-19) pandemic crisis has affected patients 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 tele-pharmacy.[11] It has been reported that pharmacist services using the ICT were at least as effect as face-to-face services, and reduced potential side effects and hospital admissions in outpatient populations with chronic diseases.[12–14] Therefore, this study aims to analyse the effect of an integrated tele-pharmacy service involving a customised mobile device compared to 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 integrated pharmaceutical care service using a customised mobile device for 282 patients with RA with the usual service by community pharmacists (figure 1 and 2). Participants will be recruited from a tertiary hospital, the Daegu Catholic University Medical Center (DCMC) in Daegu, Republic of Korea. The integrated pharmaceutical care service will be provided with monthly telephone calls and irregular text messages by clinical pharmacists in the DCMC, and supplemented with a smartphone application developed for patients with RA (that is, MediRA®). The investigators and participants will be opened to group allocation during the experiments due to the characteristics of this service intervention study. The study will follow the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) and the Consolidated Standards of Reporting Trials (CONSORT).[15, 16]

Participants and setting

Patients who meet the following criteria will be invited to participate in our study: (1) aged 18 years or older; (2) 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 Janus kinase (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 randomization; 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 by the researchers to participate in the study. Patients will attend a study explanation session and be provided a written consent to participate before enrolling in the study (appendix 1).

Participants recruitment

The patients will be recruited from the outpatient clinics and wards of the Rheumatology Department at the DCMC via posted flyers and/or word of mouth by physicians or research nurses. Recruitment posters will be provided in outpatient clinics and wards and include the overall information on the research contents and purpose for the patients. 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 with written informed consent after being provided with sufficient information by researchers. The subjects will be asked to fill out the consent form by themselves to minimise the possibility of forced or unfair effects. The language used by the researchers in the process of obtaining consent will

be consistent with the language understood by the subject.

Randomisation

The participants providing signed consent will be randomly assigned to either of the two arms with a 1:1 allocation ratio using a computer-generated list by the sealed envelope™ (https://www.sealedenvelope.com/) with a block size of 6. Randomisation will occur in the order of consent. It has two parallel arms, that is, a control or usual care (UC) group and an intervention or tele-pharmacy care (TC) group. Participants will be informed of their assigned group within 7 days after randomisation by the clinical pharmacists in the DCMC or research coordinators.

Interventions

The participants randomised to the TC group will receive the 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 and medication/disease history of the patients in the electronic medical records (EMR), and then call the participants every month for medication counselling. The monthly counselling will be conducted according to a standardised guideline of tele-pharmacy services for patients with RA which includes the following: (1) medication review to collect the patient's entire medication information such as prescription drugs from other hospitals, and over-the-counter drugs as well as 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, nonadherence, and acute care utilization such as emergency rooms (ERs) or hospitalisation in the past month.[17] Causal relationship of the

adverse reaction with the medicines will be assessed based on the Naranjo algorithm, and the following adverse reactions will be considered as serious adverse events (SAEs): death, life threatening event, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, other important medical events.[18, 19] The nonadherence will be evaluated by conducting a survey such as the Korean version of the compliance questionnaire-rheumatology (K-CQR) and asking the patients about the number of drugs for the management of RA left.[20] The severity of the identified DRPs will be assessed using the Severity Categorization for Pharmaceutical Evaluation (SCOPE) criteria, among which the information with a severity of level IV or higher is provided to the physician.[21] The pharmacists will be provided with a manual for the integrated mobile pharmaceutical services and a case report form (CRF). The MediRA app, a customised mobile application developed for this study, will also be installed on the smartphone of the participants with the help of the installation guide and the coordinator (figure 3). The app contains the following medication information for each drug listed in table 1 among drugs prescribed at the DCMC for the treatment of RA: generic name, ingredient, picture of 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 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] Researchers can provide the customised information of the drugs which the participants in the TC group will be taking, and set an alarm for non-daily medications (that is, methotrexate, biological DMARDs) for participants in the TC group using the app. In addition, the patients can get the information through text or voice whenever they need and send a text message or call the clinical pharmacists using the app if they have any questions or notice any side effects. After the

monthly tele-pharmacy service, the participants will be notified of the next schedule of the service, and the following information will be recorded on the CRF by the pharmacist: initial of the pharmacist's name, date and time of the service, and patient's enquiries and answers.

Table 1. Drug list in the MediRA app.

Category	Ingredient	Formulation	Dosage
Conventional synthetic DMARDs	Methotrexate	Tablet	2.5 mg/tab
	Leflunomide	Tablet	10 mg/tab
	Sulfasalazine	Tablet	500 mg/tab
	Hydroxychloroquine sulfate	Tablet	100 mg/tab; 150 mg/tab; 200 mg/tab; 300 mg/tab
	Bucillamine	Tablet	100 mg/tab
	Azathioprine	Tablet	25 mg/tab; 50 mg/tab
	Cyclophosphamide	Tablet	50 mg/tab
	Microemulsion cyclosporine	Capsule	25 mg/cap
	Tacrolimus hydrate	Capsule	0.5 mg/cap; 1 mg/cap
Biological DMARDs	Etanercept	Vial	25 mg/vial
		Pen injector	50 mg/mL
		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/tab
	Baricitinib	Tablet	2 mg/tab; 4 mg/tab
	Upadacitinib	Extended-release tablet	15 mg/tab
NSAIDs	Nabumetone	Tablet	500 mg/tab
	Aceclofenac	Tablet	100 mg/tab
	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/tab; 325 mg, 37.5 mg/tab
		Extended-release tablet	325 mg, 37.5 mg/tab; 650 mg, 75 mg/tab
Glucocorticoids	Prednisolone	Tablet	5 mg/tab
	Methylprednisolone	Tablet	4 mg/tab
	Dexamethasone	Tablet	0.5 mg/tab
	Triamcinolone	Tablet	1 mg/tab; 2 mg/tab; 4 mg/tab
	Deflazacort micronized	Tablet	6 mg/tab

Abbreviation: DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs.

Participants in the control group will receive usual care from local community pharmacists

without the implementation of an integrated pharmaceutical care model. The usual care mainly consists of dispensing prescribed drugs and 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 patients in this study.

Outcome measures

Primary outcomes measurements

The primary outcome of this study will be the changes in health-related quality of life (HRQoL) as measured by the Korean version of the EuroQoL's five-dimensional questionnaire (K-EQ-5D) at 6 months compared to baseline.[26, 27] HRQoL in patients 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 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 got a permission of its use from the EuroQol Research Foundation.[31] The questionnaire consists of two parts: a descriptive system (EQ-5D-5L) and visual analogue scale (EQ-5D-VAS). The EQ-5D-5L describes the 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 zero indicates the worst imaginable health state and 100 reflects the best imaginable health state.[31, 32] We applied a Korean translation of the EQ-5D that was validated for cultural authenticity.[27]

Secondary outcomes measurements

Secondary outcomes will be the following: (1) changes in scores of K-CQR at 3 and 6

months compared to baseline measurements; (2) changes in scores of medication knowledge and attitude at 3 and 6 months compared to baseline; (3) changes in scores of the Korean version of the pharmacy service questionnaire (K-PSQ) at 6 months compared to 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 to baseline; and (5) frequency of acute care utilisation over 6 months.[20, 33]

Compliance to medication therapy is important to reach the desired therapeutic outcome for the management of RA.[6] The compliance questionnaire-rheumatology (CQR) is a rheumatology-specific instrument that measures patient compliance to antirheumatic drug regimens and identifies factors for the suboptimal patient compliance with 19 items.[34] The participants will complete the questionnaire in their own environment at baseline, and 3 and 6 months using the validated K-CQR.[20] Medication knowledge and attitude of the patients will be evaluated at baseline, and 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, and 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 6 months.[33] The clinical parameters (that is, ESR and CRP levels, pain score, and number of joint involvements) will be analysed through chart review at baseline, and 3 and 6 months by the clinical pharmacists. If there is missing information in 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 assessment number and assess time of the app for each participant in the TC group. Satisfaction with the mobile app will also 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 6 months, and some of them (that is, K-CQR, medication knowledge, and clinical parameters) will be additionally collected at 3 months. 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 patient interviews. The medications are categorised as follows: conventional synthetic DMARDs, biological DMARDs, JAK inhibitors, NSAIDs, glucocorticoids, dietary supplements, and others. Information such as ingredients, generic name, dosage, administration, and duration of administration will also be collected. Vital signs (blood pressure and heart rate) and laboratory results related to dosage or adverse drug reactions (ADRs) (that is, complete blood count such as white blood cell (WBC) count, absolute neutrophil count (ANC), haemoglobin, and platelet; renal and hepatic function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, serum creatinine (SCr), blood urea nitrogen (BUN), and creatinine clearance (CrCL); fasting glucose; and total cholesterol level) or disease activity (that is, ESR, CRP, or NRS) will be collected by EMR review.

Table 2. Schedule of enrolment, interventions and assessments (SPIRIT).

	Enrol-	Allo-	Post-allocation

	ment	cation						
Time point	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6
Study week	-2	0	4 ± 1	8 ± 1	12 ± 1	16 ± 1	20 ± 1	24 ± 1
Enrolment								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Interventions								
Tele-pharmacy care		X [a]	X	X	X	X	X	X
Usual care		●	– – –	– – –	– – –	– – –	– – –	●
Assessments								
Demographic information	X							
K-EQ-5D	X							X
K-PSQ	X							X
K-CQR	X				X			X
Medication knowledge	X				X			X
CRP	X				X			X
ESR	X				X			X
VAS	X				X			X

Joint involvement	X			X			X
ER visits/ hospitalization		—	—	—	—	—	—
AEs		—	—	—	—	—	—
Mobile application utilization		X	X	X	X	X	X
Mobile application satisfaction							X

Abbreviation: 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-5 dimension questionnaire; K-PSQ, Korean version of the patient satisfaction questionnaire; VAS, visual analogue scale.

[a] Within a week after randomisation

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.[36] 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 have difficulties in taking an online survey, the 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 subjects, and those with access to the study data will be limited to the investigators of this study. Information recorded in the CRF will be entered into a spreadsheet with a password by at least two study coordinators, and 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. Personal information (such as subject numbers, prescription drugs, and more) is collected during the process of using mobile applications/apps, but no information is collected to identify patients. Mobile device information (mobile carrier information, device information), access records, and access times, which are automatically generated and collected during the mobile service, will be used only for research purposes described above and stored in a separate password-protected database. At the time of publication of the findings, no identifiable data will be provided. After processing and analysis, all data will be published in a consolidated form.

The data obtained in this study may continue to evolve in the future, so case record form, survey results sheets, and data stored in the mobile application/app database will not be discarded until five years after completion of the study and all data will be password-protected or locked under the supervision and responsibility of the principal researcher.

Sample size

We estimated that an overall sample size of 233 patients 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 to the control group, with a standard deviation of 13.9 at a two-sided alpha level of 0.05.[37, 38] Assuming that the dropout rate is 10%, we will need to enrol approximately 256 patients (128 people per group).

Consideration of safety for the subjects

Considering the objective of this study, it is not expected that there will be any particular risk to the study participants. The subjects 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 judgment of the investigators (such as cognitive impairment), or significant non-compliance with the study protocol. Subjects will be informed that they can withdraw their participation voluntarily at any time, and that even if the study is discontinued, the pharmacist services will be continuously provided as before and there are no disadvantages in the discontinuation of the study.

Statistical analysis

Intent-to-treat (ITT) and per-protocol (PP) analyses will be conducted for all outcomes for all participants recruited prospectively, and for patients who completed the study according to the protocol, respectively. All protocol deviation or violation 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 standard deviations (SD) for continuous parametric data, and medians and interquartile range (IQR) for non-parametric variables. Fisher's exact and chi-square tests will be used to compare categorical data and unpaired t and Mann-Whitney tests will be used to compare continuous data. Spearman's rank correlation coefficients will be used to identify bivariate relationships between HRQoL at baseline and at six-month follow-up. Correlation coefficients higher than 0.5, will be interpreted as having a correlation, whereas those lower than 0.5 as little relationship. Multiple imputation will be used to handle missing outcome data. A subgroup

analysis of patients with and without first diagnosis of RA will be performed. Statistical significance has been set at a two-sided p-value < 0.05, and data analysis and computation will be conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL) or SAS version 9.4 (SAS Institute, Cary, NC, USA). Analysis will be done by the research statistician, who will be blind to study groups.

Patients and public involvement

Patients and/or the public were and will not be involved in the design, conduct, or reporting of the study. During the study, patients will be assessed for 6 months of the study period, but they will not be able to assess their CRF. The patients 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 ICH E6 Good Clinical Practice (GCP) guidelines for the planning and conduct of 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 (CRIS), Korea Disease Control and Prevention Agency (registration no. KCT0006508, 27 August, 2021).[39] 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.

Acknowledgements

We acknowledge Jihyeon Im and Hyojeong Lee for assistance in trial set up at the college of pharmacy, Daegu Catholic University and the division of rheumatology, Daegu Catholic University School of Medicine, respectively. We would like to express our gratitude to Bongseo Jang from college of pharmacy, Daegu Catholic University for development of the MediRA application.

Author Statement

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 JYC provided critical revision of the manuscript. All authors discussed and helped to improve the protocol, and read and approved the final manuscript.

Competing Interests

None declared.

Funding Information

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2019R1G1A1100325).

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FIGURE LEGENDS

Figure 1. PROUD study design. Abbreviations: 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-5 dimension questionnaire; K-PSQ, Korean version of the patient satisfaction questionnaire; VAS, visual analogue scale.

Figure 2. Flow diagram of the study design

Figure 3. Patient's guide for an installation of a MediRA app, a personalised smartphone application for patients with rheumatoid arthritis

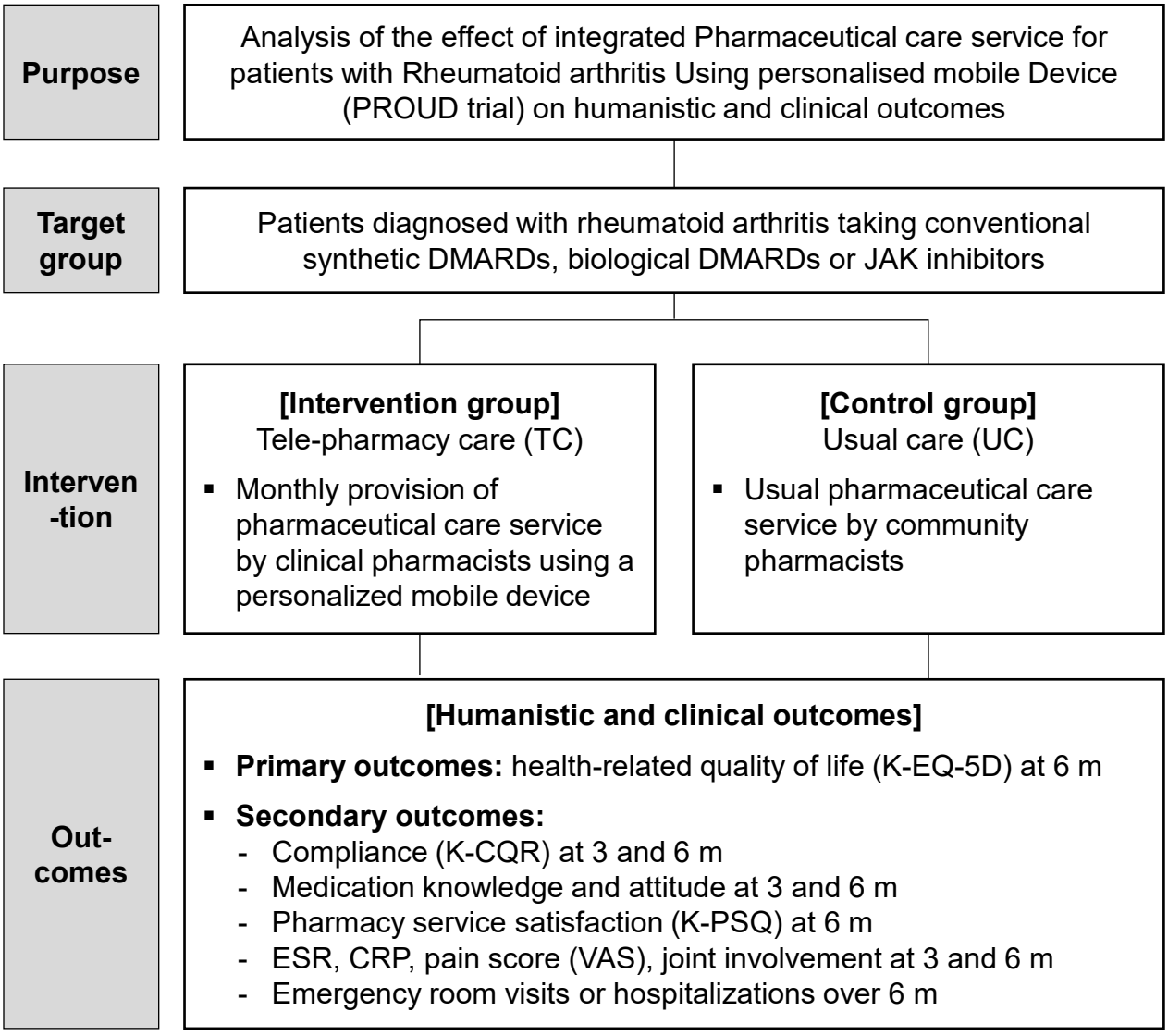
Purpose
Analysis of the effect of integrated Pharmaceutical care service for patients with Rheumatoid arthritis Using personalised mobile Device (PROUD trial) on humanistic and clinical outcomes
Target group
Patients diagnosed with rheumatoid arthritis taking conventional synthetic DMARDs, biological DMARDs or JAK inhibitors
Interven -tion
[Intervention group]
Tele-pharmacy care (TC)
Monthly provision of pharmaceutical care service by clinical pharmacists using a personalized mobile device
[Control group]
Usual care (UC)
Usual pharmaceutical care service by community pharmacists
Out- comes
[Humanistic and clinical outcomes]
Primary outcomes: health-related quality of life (K-EQ-5D) at 6 m
Secondary outcomes:
- Compliance (K-CQR) at 3 and 6 m
- Medication knowledge and attitude at 3 and 6 m
- Pharmacy service satisfaction (K-PSQ) at 6 m
- ESR, CRP, pain score (VAS), joint involvement at 3 and 6 m
- Emergency room visits or hospitalizations over 6 m

Figure 1

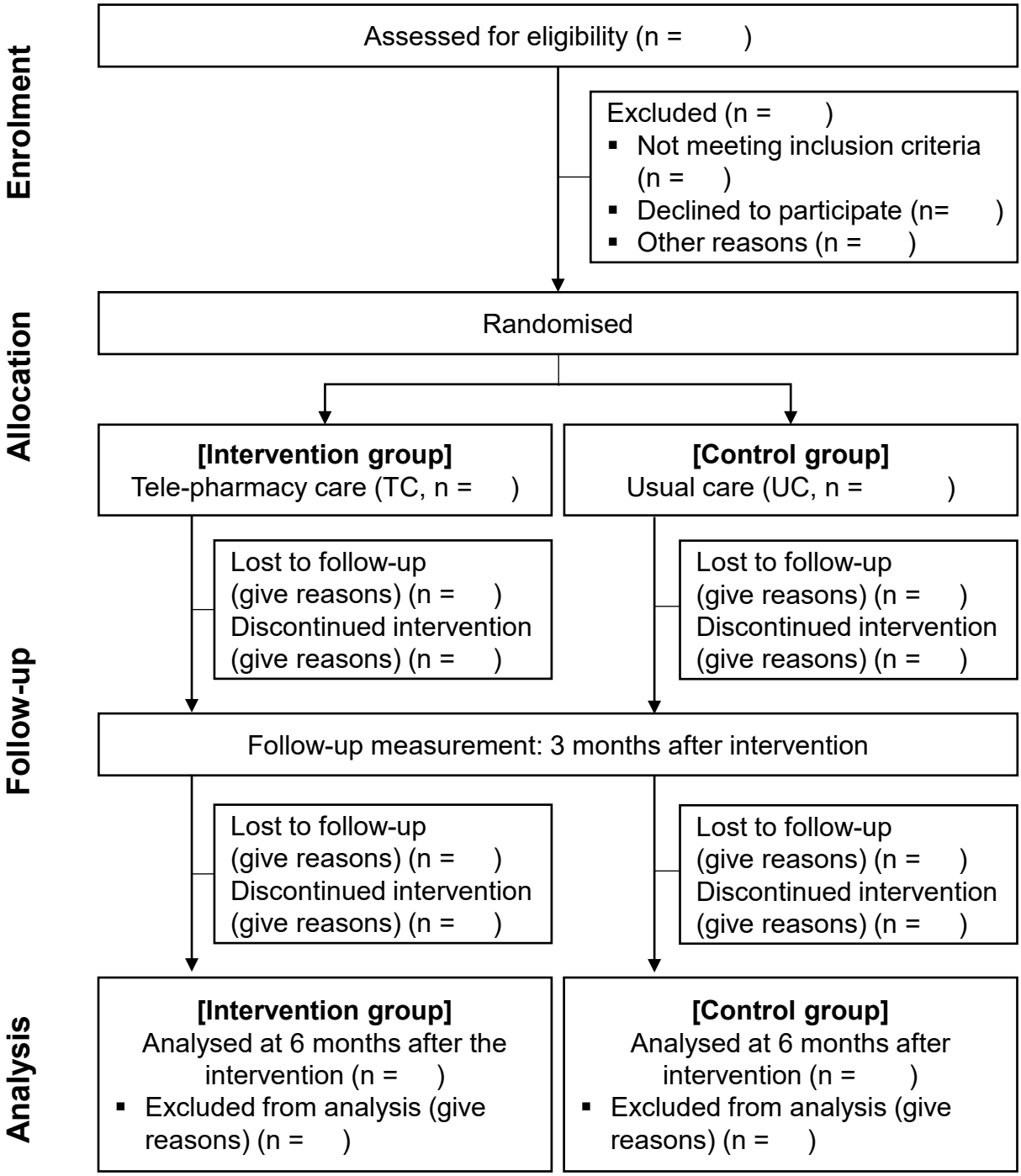
Enrolment
Assessed for eligibility (n =)
Excluded (n =)
Not meeting inclusion criteria (n =)
Declined to participate (n=)
Other reasons (n =)
Allocation
Randomised
[Intervention group]
Tele-pharmacy care (TC, n =)
[Control group]
Usual care (UC, n =)
Follow-up
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Follow-up measurement: 3 months after intervention
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Analysis
[Intervention group]
Analysed at 6 months after the intervention (n =)
Excluded from analysis (give reasons) (n =)
[Control group]
Analysed at 6 months after intervention (n =)
Excluded from analysis (give reasons) (n =)

Figure 2

Figure 3

(Version 2.0)

대상자 설명문

1. 연구과제명

류마티스관절질환자 대상 원격 모바일 약료서비스 성과분석 연구

2. 연구책임자

대구가톨릭대학교병원 류마티스내과 교수 김 지 원

3. 개요

이 연구는 비대면 서비스에 대한 사회적 요구도가 높은 상황에서, 전문 임상약사의 표준화된 원격 모바일 약사서비스 제공이 류마티스관절염 환자의 약물관리 효과에 미치는 영향을 평가하기 위한 연구입니다. 귀하는 류마티스관절염 치료를 위한 새로운 약물을 투여하기 시작하였기에 이 연구에 참여하도록 권유 받았습니다. 이 연구를 수행하는 대구가톨릭대학교병원 소속 연구책임자(김지원 교수) 혹은 연구담당자(박지은 약사, 070-8015-6040)가 귀하에게 이 연구 참여 과정에 대하여 설명해 줄 것입니다 이 연구는 자발적으로 참여 의사를 밝히신 분에 한하여 수행될 것이며, 귀하께서는 본 임상 연구에 참여 의사를 결정하기에 앞서, 본 임상연구가 왜 수행되고, 귀하의 정보가 어떻게 사용될지, 본 임상연구가 어떤 것을 포함하고 있는 지와 가능한 이점, 위험, 불편함은 무엇인지에 대하여 이해하는 것이 중요합니다. 다음의 설명을 신중하게 시간을 가지고 주의 깊게 읽으시기 바라며, 필요하시면 귀하의 주치의 또는 가족이나 친구들과 상의하시기 바랍니다. 만일 어떠한 질문 사항이 있으시면 연구자가 자세하게 설명해 줄 것입니다.

4. 연구의 목적 및 배경

관절 활막의 지속적인 염증 반응을 특징으로 하는 류마티스관절염은 일반적으로 관절 손상을 예방하고 골밀도를 보존하기 위해 장기적 약물치료가 필수적입니다. 약물의 치료효과를 높이고 합병증을 관리하기 위해 의사, 간호사 및 임상약사에 의한 통합적인 보건의료서비스에 대한 요구도가 높아졌습니다. 아울러, 최근 코로나 19 의 대규모 확산 사태와 함께 약물요법 관리를 위한 비대면 약사서비스 제공이 중요하게 고려되고 있습니다.

본 연구에서는 류마티스 관절염 환자에서의 효과적인 약물요법 관리를 위한 전문 임상약사의 표준화된 원격 모바일 약사서비스 제공이 질병 및 약물관리에 미치는 효과를 평가하고자 합니다.

5. 연구 약물/기기

본 임상시험은 비대면 약물사용교육 서비스가 중심이 되므로, 이 연구에 참여함으로써 귀하에게 새롭게 투여되는 약물이나 기기는 없습니다. 귀하가 본 임상연구에 참여하는 동안 류마티스관절염을 치료하기 위해 받게 되는 모든 약물요법 및 치료적 처치는 연구참여 여부와 상관없이 의학적 판단에 따라 이루어집니다.

6. 대안 치료 (임상시험 이외의 다른 대체 가능한 치료법)

귀하가 본 연구에 참여하기를 원하지 않는다면, 귀하의 연구 담당의사는 귀하에게 적절한 치료법에 대해 설명할 수 있으며 귀하는 모든 표준 요법들로 치료받으실 수 있습니다.

7. 연구방법에 관한 설명

(1) 절차 또는 치료

본 연구에 참여한 대상자는 무작위배정을 거쳐 1:1 의 비율로 원격 모바일 약사서비스군(시험군)과 기존 약사서비스군(대조군)으로 나누어집니다. 두 군 모두 기존의 치료와 처치, 검사를 받게 되며, 시험군의 환자는 추가적으로 본 연구의 계획에 따라 원격 모바일 약사서비스를 제공받게 됩니다. 1 개월 간격으로 유선으로 약사가 귀하에게 전화를 할 것이며, 약사는 복용 중인 약물을 조사하고 복약상담과 복약순응도 향상을 위한 교육을 제공할 것입니다. 평상시에 귀하는 모바일 어플리케이션을 활용하여 환자별로 맞춤형으로 제공된 약물정보를 토대로 약물복용과 관련하여 궁금한 내용을 확인할 수 있으며, 삶의 질과 복약순응도는 설문으로 평가하게 됩니다.

방문일정	설문조사
방문 1 (외래 등록 시)	삶의 질, 복약순응도, 약물인지도, 환자만족도
방문 2 (연구시작 3 개월 ± 7 일 후)	복약순응도, 약물인지도
방문 3 (연구시작 6 개월 ± 7 일 후)	삶의 질, 복약순응도, 약물인지도, 환자만족도

(2) 연구기간 및 대상자 참여 기간, 예상 대상자 수(전체 대상자 수/본원 대상자 수)

본 임상연구는 대구가톨릭대학교병원 생명윤리위원회의 승인일로부터 2022.6.30.까지 진행됩니다. 본 임상연구에 참여하는 대략의 대상자 수는 약 280 여명으로 각 대상자의 연구참여 예상기간은 무작위배정 이후 최소 6 개월입니다.

(3) 시험 제한 사항 및 대상자 의무

본 연구에 참여하는 동안 본 기관에서 처방하는 약물 또는 관리 외에 별도의 다른 약물을 사용(복용하거나, 주사로 투여하거나, 피부에 바르는 등)할 경우에는 반드시 연구담당자에게 알려주십시오. 연구담당자의 지시에 따르지 않거나, 추적관찰에 실패할 경우 귀하는 귀하의 동의 없이도 본 연구의 참여로부터 제한될 수 있습니다.

(4) 대상자 선정, 제외기준

- **대상자 선정기준**

① 대구가톨릭대학병원 류마티스내과를 방문하는 18 세 이상 외래 환자 중 류마티스 관절염으로 진단받고 다음과 같은 DMARD 를 1 개 이상 투여하는 자

- Conventional DMARDs: Hydroxychloroquine, methotrexate, sulfasalazine, bucillamine, leflunomide
- 생물학적 DMARDs (피하주사제): etanercept, adalimumab, golimumab
- JAK 억제제: tofacitinib, baricitinb

② 무작위배정 시점에 새로운 약물(DMARD, 스테로이드제, 또는 진통제)를 투여하기 시작한 자
③ 모바일 기기(스마트폰 등)을 소지한 자
④ 연구 참여에 동의한 자

- **대상자 제외기준**

① 인지능력 저하 등으로 인해 서면 또는 면접설문 응답이 어려운 환자
② 중증의 전신 또는 악성 질환자 (ECOG 2점 이상, 악성 종양을 진단받고 치료 중인 자)
③ 모바일 기기에 복약순응도 향상도구(동 연구에서 제작한 별도의 어플리케이션 또는 앱)이 설치되지 않거나 설치에 동의하지 않는 자
④ 멀티미디어 메시지 서비스(Multimedia Messaging Service, MMS)를 이용한 복약정보 제공에 동의하지 않는 자
⑤ 기타 연구진이 연구 참여에 적절하지 않다고 판단한 자

8. 대상자에게 예견되는 이상반응, 위험과 불편함

본 연구는 비대면 약물사용교육 서비스가 중심이므로 참여하는 대상자에게서 연구 수행 시 진행되는 모든 검사나 교육은 침습적이거나 위험하지 않습니다. 따라서 본 연구 참여로 인해 나타날 것으로 예상되는 추가적인 부작용이나 불편은 없습니다. 단, 본 연구에의 참여로 인해 받게 되는 복약상담 및 교육서비스에 다소간의 시간이 소요될 수 있습니다

9. 대상자에게 예견되는 이득

귀하가 본 연구에 참여함으로써 귀하에게 의학적 혜택이 보장되는 것은 아닙니다. 본 연구에 참여하는 동안 받게 되는 모든 약물요법 및 치료적 처치는 연구참여 여부와 상관없이 동일합니다. 그러나, 전문임상약사에 의해 추가적인 비대면 약물사용교육 서비스를 제공받음으로써 효과적인 약물요법 관리가 가능하고 약물의 효과를 높일 수 있을 것으로 기대됩니다.

10. 연구 관련 새로운 정보의 지속적 제공

본 연구 기간 중 귀하의 시험 참여 여부를 결정하는데 영향을 줄 수 있는 새로운 유의한 정보가 얻게 되는 즉시 귀하 또는 귀하의 대리인에게 알려 드릴 것입니다.

11. 금전적 지급

본 연구 참여 중 실시되는 모든 약물요법 및 검사 과정은 연구에 참여하지 않더라도 받아야 하는 것으로 약제 및 검사비에 대한 보상은 없으며 연구에 참여함으로써 대상자에게 추가적으로 발생하는 별도의 비용은 없습니다. 본 연구의 참여로 인해 소요되는 시간에 대한 보상으로 첫 방문과 연구시작 6 개월째 마지막 방문 시 각각 1 만원의 교통비가 지급될 예정입니다.

12. 피해발생 시 대상자 보상(의료적 치료/보상)

본 연구는 기존 진료에서 진행되고 있는 시술 또는 치료 방법(의약품, 의료기기 포함)에 추가로 약사에 의한 비대면 약물요법관리가 이루어지는 연구로서, 의학적으로 판단하였을 때 동 연구로 인한 추가적 위험이 기존 진료 과정에서 진행되고 있는 시술 또는 치료 방법보다 현저하지 않습니다. 따라서 이 연구로 인해 대상자가 추가적으로 입게 되는 신체적, 정신적 위해 및 특이 손상은 없을 것으로 예측됩니다. 대상자들에게는 통상적인 진료 과정에서 이루어지는 안전 보호 대책이 적용될 것이며, 연구 시작 전 연구대상자들에게 해당 연구의 목적과 방법 등에 대해 충분한 정보가 제공될 것입니다.

13. 비밀 보장

연구대상자의 신원을 파악할 수 있는 기록은 비밀로 보장될 것이며, 연구의 결과가 출판될 경우 연구대상자의 신원은 비밀상태로 유지될 것입니다. 연구대상자 번호는 환자의 병원등록번호가 아닌 각 환자마다 임의의 번호를 할당하여 관리할 것이며, 연구를 위해 수집되는 모든 정보와 자료는 잠금장치가 있는 연구책임자가 지정한 곳에 보관할 것입니다. 연구관련 기록은 연구완료시점부터 3 년간 보관하며, 보관기간이 지난 문서나 파일은 개인정보보호법에 따라 파기할 것입니다.

14. 의무기록의 열람

임상연구의 책임연구자, 연구담당자, 공동연구자, 생명윤리위원회(IRB)는 관계 법령에 따라 연구의 절차와 자료의 품질을 검증하기 위하여 대상자의 신상에 관한 비밀이 보호되는 범위에서 대상자의 연구기록을 열람할 수 있습니다. 대상자 또는 대상자의 대리인이 서명한 동의서에 의하여 이러한 자료의 열람이 허용될 것입니다.

15. 자발적 참여

본 연구에 참여하시는 것은 귀하에게 달려 있습니다. 귀하는 언제든지 시험에 참여하지 않기로 결정할 수 있고 또한 시험을 그만 둘 수 있습니다. 귀하가 본 연구에 참여하지 않아도 아무런 불이익을 받지 않으며 귀하의 결정은 향후 귀하가 진료를 받는 것에 영향을 미치지 않습니다.

16. 연구의 중지

연구담당 약사의 지시를 따르지 않거나, 정해진 기간에 유선을 통한 연락이 되지 않아 추적관찰에 실패한 경우, 연구자의 판단 하에 더 이상 연구 참여가 부적합한 경우(예: 인지능력 상실 등)에 귀하는 귀하의 동의 없이 본 연구의 참여가 제한될 수 있습니다.

17. 개인정보 제공에 관한 사항

본 동의서에 서명함으로써 귀하는 연구진이 귀하의 개인정보 및 민감정보를 수집하고 사용하는데 동의하게 됩니다.

- **개인 및 민감정보의 수집·이용 목적**

  개인정보: 귀하의 이름, 주소, 휴대전화번호, 출생연도, 성별, 이메일주소

  민감정보: 류마티스관절염 유병기간 및 약물복용기간, 동반질환, 흡연력, 키, 체중, 혈압, 맥박수, 임상검사정보, 응급실 방문 또는 입원 정보, 설문조사 정보(건강관련 삶의 질, 복약순응도, 약물인지도, 약사서비스만족도 등), 모바일 기기 정보(이동통신사 정보, 단말기 정보), 쿠키, 접속기록, 접속시간

  수집·이용 목적: 귀하의 성명, 성별, 나이, 병원등록번호, 임상연구 과정에서 발생하는 진료기록 및 자료 등 건강 관련 정보는 연구 관련 임상 정보의 획득 및 확인을 위한 목적으로만 수집되며 이용됩니다.

- **개인 및 민감정보의 보유 및 이용 기간**

  귀하의 개인 및 민감정보는 연구를 위해서만 사용되며 수집된 개인정보는 개인정보 보호법에 따라 적절히 관리됩니다. 수집된 개인정보 및 민감정보는 연구 결과보고 후 3 년간 보관 후 폐기합니다.

- **동의를 거부할 권리가 있다는 사실 및 동의 거부에 따른 불이익이 있는 경우에는 그 불이익의 내용**

  귀하는 위 개인 및 민감정보 수집 및 이용, 제공에 대한 수락 여부를 자유롭게 결정할 수 있습니다. 귀하가 개인 및 민감정보 수집 및 이용, 제공에 수락하지 않는 경우에도 귀하에 대한 진료와 처방에 어떠한 불이익도 발생하지 않습니다.

18. 연구 관련 책임자 및 연락처

귀하는 연구책임자 혹은 연구담당자(박지은 약사/070-8015-6040)에게 임상연구 기간 중에 언제든지 추가적인 정보를 요청할 수 있습니다. 또한 귀하는 연구 대상자로서의 귀하의 권리에 대해 의문이 있을 경우 대구가톨릭대학교병원 생명윤리위원회(053-650-3062, 3063)로 연락할 수 있습니다.

(Version 2.0)

대상자 동의서

연구과제명: 류마티스관절질환자 대상 원격 모바일 약료서비스 성과분석 연구

1. 본인은 임상연구에 대해 구두로 설명을 받고 상기 대상자 설명문을 읽었으며 담당연구원과 이에 대하여 의논하였습니다.
2. 본인은 위험과 이득에 관하여 들었으며 나의 질문에 만족할 만한 답변을 얻었습니다.
3. 본인은 이 연구에 참여하는 것에 대하여 자발적으로 동의합니다.
4. 본인은 이후의 치료에 영향을 받지 않고 언제든지 연구의 참여를 거부하거나 연구의 참여를 중도에 철회할 수 있고 이러한 결정이 나에게 어떠한 해가 되지 않을 것이라는 것을 알고 있습니다.
5. 본인은 이 설명서 및 동의서에 서명함으로써 의학 연구 목적으로 나의 개인정보가 현행 법률과 규정이 허용하는 범위 내에서 연구자가 수집하고 처리하는데 동의합니다.
6. 본인은 개인정보 및 민감정보의 수집, 이용에 대한 설명을 이해하고 이에 동의합니다.

본인은 본 연구의 수행에 따른 개인정보의 수집 및 이용에 동의합니다.	예□ 아니오□
본인은 본 연구의 수행에 따른 민감정보의 수집 및 이용에 동의합니다.	예□ 아니오□

7. 본인은 이 동의서 사본을 받을 것을 알고 있습니다.

대상자 성명	서명	날짜 (년/월/일)
법정대리인 성명 (대상자와의 관계:)	서명	날짜 (년/월/일)
입회인 성명 (해당되는 경우)	서명	날짜 (년/월/일)
성명 연구책임자 또는 연구책임자의 위임을 받은자	서명	날짜 (년/월/일) * 대리인이 서명하는 경우 대리인임을 확인 할 수 있는 서류 첨부

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2, 19

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#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	NA
Roles and responsibilities: committees	#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)	NA

Introduction

Background and rationale	#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	5–6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5–6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	6–7

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8–12
Interventions: modifications	#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)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8–9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#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	12–13
Participant timeline	#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)	14–16

Sample size	#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	17
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7–8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#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	8
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	NA
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7–8

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#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	12-17
Data collection plan: retention	#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	8-12, 18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	16-17

		(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	
Statistics: outcomes	#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	18-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis population and missing data	#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)	18
Methods: Monitoring			
Data monitoring: formal committee	#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	NA
Data monitoring: interim analysis	#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	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing	8-9

		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	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
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)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	16-17

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-17
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	18
Dissemination policy: trial results	#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	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	NA

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061917.R1
Article Type:	Protocol
Date Submitted by the Author:	26-May-2022
Complete List of Authors:	Park , Ji-Eun ; Daegu Catholic University; Daegu Catholic University Medical Center Lee , Ju-Eun ; Daegu Catholic University Medical Center Moon , Bo-Kyung; Daegu Catholic University Medical Center Lee, Hwajeong ; Daegu Catholic University School of Medicine Park , Sung-Hoon ; Daegu Catholic University School of Medicine Kim, Seong-Kyu; Daegu Catholic University School of Medicine, Department of Internal Medicine Choe, Jung-Yoon; Daegu Catholic University School of Medicine, Rheumatology Kim, Ji-Won ; Daegu Catholic University School of Medicine Song, Yun-Kyoung; Daegu Catholic University, College of Pharmacy
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Communication, Evidence based practice, Health services research, Medical education and training
Keywords:	RHEUMATOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS

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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Word count 3,737

ABSTRACT

Introduction Rheumatoid arthritis (RA) generally requires lifelong treatment; however its medication complexity might affect nonadherence. Pharmacist-led telehealth services were as effective as face-to-face services, and reduced potential side effects in outpatient with chronic diseases. This study aims to analyse the effect of a tele-pharmacy service with a customised mobile device in comparison to 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 (tele-pharmacy 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 five-dimensional questionnaire at 6 months compared to baseline. The secondary outcomes will be the changes in the followings: scores of the Korean version of the compliance questionnaire-rheumatology and medication knowledge at 3 and 6 months compared to baseline; scores of the Korean version of the pharmacy service questionnaire at 6 months compared to baseline; clinical parameters such as erythrocyte sedimentation rate, C-reactive protein level, and pain score at 3 and 6 months compared to baseline; frequency of acute care utilisation over 6 months. Analysis will be carried out with intent-to-treat and per-protocol principles.

Ethics and dissemination The study protocol was reviewed and approved by the institutional review board of Daegu Catholic University Medical Center (IRB no. CR-21-082-

L, 14 July, 2021). The study findings will be published in peer-reviewed journals.

Trial registration number KCT0006508

Keywords antirheumatic, arthritis, tele-pharmacy, tele-communication, humanistic

Strengths and limitations of this study

- This study will evaluate the effect of a tele-pharmacy service in comparison to 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 Korean version of the EuroQoL's five-dimensional questionnaire at 6 months compared to 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, 2] 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 nonadherence and therapeutic failure.[3, 4] Furthermore, intentional and unintentional nonadherence with RA drugs accounted for 24.2% and 31.8%, respectively, which might be due to the medication complexity or low confidence in pharmacotherapy.[4] 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.[5, 6]

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.[7, 8] Mary et al.[8] 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 to 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 (ICT) at its core, tele-pharmacy services appear to be an innovative way to deliver pharmacist care services through the use of telecommunications.[9, 10] The coronavirus

disease 2019 (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 tele-pharmacy.[11] 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.[12–14] Therefore, this study aims to analyse the effect of a tele-pharmacy service involving a customised mobile device in comparison to 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 (Figure 1 and 2). Participants 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 concealed from the investigators and participants during the experiments. The study will follow the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) and the Consolidated Standards of Reporting Trials (CONSORT).[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 randomization; 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 tele-pharmacy service using telecommunications due to hearing impairment. Participants will attend a study explanation session and be provided with a written consent to participate before enrolling in the study (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 tele-pharmacy 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 (EMR), and the participants will be called every month for medication counselling. The monthly counselling will be conducted according to a standardised guideline of tele-pharmacy 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, nonadherence, and acute care utilization such as emergency rooms (ERs) 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 (SAEs): death, a life threatening event, hospitalization (either initial or extended), disability or permanent damage, congenital anomaly or birth defect, and other significant medical events.[18, 19] The nonadherence 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 (SCOPE) 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 tele-pharmacy services and a case report form (CRF). After the monthly tele-pharmacy 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 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.

Table 1. Drug list in the MediRA app.

Category	Ingredient	Formulation	Dosage
Conventional	Methotrexate	Tablet	2.5 mg/tab
synthetic	Leflunomide	Tablet	10 mg/tab
DMARDs	Sulfasalazine	Tablet	500 mg/tab
	Hydroxychloroquine	Tablet	100 mg/tab; 150 mg/tab;
	sulfate		200 mg/tab; 300 mg/tab
	Bucillamine	Tablet	100 mg/tab

	Azathioprine	Tablet	25 mg/tab; 50 mg/tab
	Cyclophosphamide	Tablet	50 mg/tab
	Microemulsion cyclosporine	Capsule	25 mg/cap
	Tacrolimus hydrate	Capsule	0.5 mg/cap; 1 mg/cap
Biological DMARDs	Etanercept	Vial	25 mg/vial
		Pen injector	50 mg/mL
		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/tab
	Baricitinib	Tablet	2 mg/tab; 4 mg/tab
	Upadacitinib	Extended-release tablet	15 mg/tab
NSAIDs	Nabumetone	Tablet	500 mg/tab
	Aceclofenac	Tablet	100 mg/tab
	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/tab; 325 mg, 37.5 mg/tab

		Extended-release tablet	325 mg, 37.5 mg/tab; 650 mg, 75 mg/tab
Glucocorticoids	Prednisolone	Tablet	5 mg/tab
	Methylprednisolone	Tablet	4 mg/tab
	Dexamethasone	Tablet	0.5 mg/tab
	Triamcinolone	Tablet	1 mg/tab; 2 mg/tab; 4 mg/tab
	Deflazacort micronized	Tablet	6 mg/tab

Abbreviation: DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs.

Participants in the control group will receive usual care from local community pharmacists without the implementation of a tele-pharmacy 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 outcomes 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 to 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 zero 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.[27]

Secondary outcomes measurements

Secondary outcomes will be as follows: (1) changes in scores of K-CQR at 3 and 6 months compared to baseline measurements; (2) changes in medication knowledge scores at 3 and 6 months compared to baseline; (3) changes in validated Korean version of the pharmacy service questionnaire (K-PSQ) scores at 6 months compared to 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 to baseline; and (5) frequency of acute care utilisation over 6 months.[20, 33]

Compliance with medication therapy is important to acheive 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 analysed 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 five-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 six 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 (ADRs) (complete blood count including white blood cell (WBC) count, absolute neutrophil count (ANC), haemoglobin level, and platelet count; renal and hepatic function tests, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, serum creatinine (SCr), blood urea nitrogen (BUN), and creatinine clearance (CrCL); fasting glucose; and total cholesterol level) or disease activity (ESR, CRP, or NRS) will be collected by EMR review.

Table 2. Schedule of enrolment, interventions and assessments (SPIRIT).

	Enrol-ment	Allo-cation	Post-allocation					
Time point	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6
Study week	-2	0	4 ± 1	8 ± 1	12 ± 1	16 ± 1	20 ± 1	24 ± 1
Enrolment								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Interventions								
Tele-pharmacy		X [a]	X	X	X	X	X	X

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

Abbreviation: 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-5 dimension questionnaire; K-PSQ, Korean version of the patient satisfaction questionnaire; VAS, visual analogue scale.

[a] Within a week after randomisation

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.[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 (mobile carrier information, device information), access records, and access times, which are automatically generated and

collected during the use of the mobile service, will be used only for the research purposes described above and stored in a separate password-protected database. At the time of publication of the findings, no identifiable data will be disclosed. After processing and analysis, all the data will be published in a consolidated form.

The data obtained in this study may continue to evolve in the future; therefore, case record forms, survey results sheets, and data stored in the mobile application database will not be discarded until 5 years after the completion of the study, and all data will be password-protected or locked under the supervision and responsibility of the principal researcher.

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 to the control group, with a standard deviation of 13.9 at a two-sided alpha level of 0.05.[38, 39] 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 (PP) 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 standard deviations (SD) for continuous parametric data, and medians and interquartile range (IQR) for non-parametric variables. Fisher's exact and chi-square tests will be used to compare categorical data and unpaired t and Mann–Whitney tests 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-value <0.05, and data analysis and computation will be conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA) or SAS version 9.4 (SAS Institute, Cary, NC, USA). 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 ICH E6 Good Clinical Practice (GCP) 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 (CRIS), Korea Disease Control and Prevention Agency (registration no. KCT0006508, 27 August, 2021).[40] 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.

Acknowledgements

We acknowledge Jihyeon Im and Yoonjung Kim at the College of Pharmacy, Daegu Catholic University, and Hyojeong Lee at the Division of Rheumatology, Daegu Catholic University School of Medicine, for assistance in the set-up of the trial. We would like to express our gratitude to Bongseo Jang from the College of Pharmacy, Daegu Catholic University, for the development of the MediRA application.

Author Statement

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 JYC provided critical revision of the manuscript. All authors discussed and helped to improve the protocol, and read and approved the final manuscript.

Competing Interests

The authors declare no conflicts of interest.

Funding Information

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2019R1G1A1100325).

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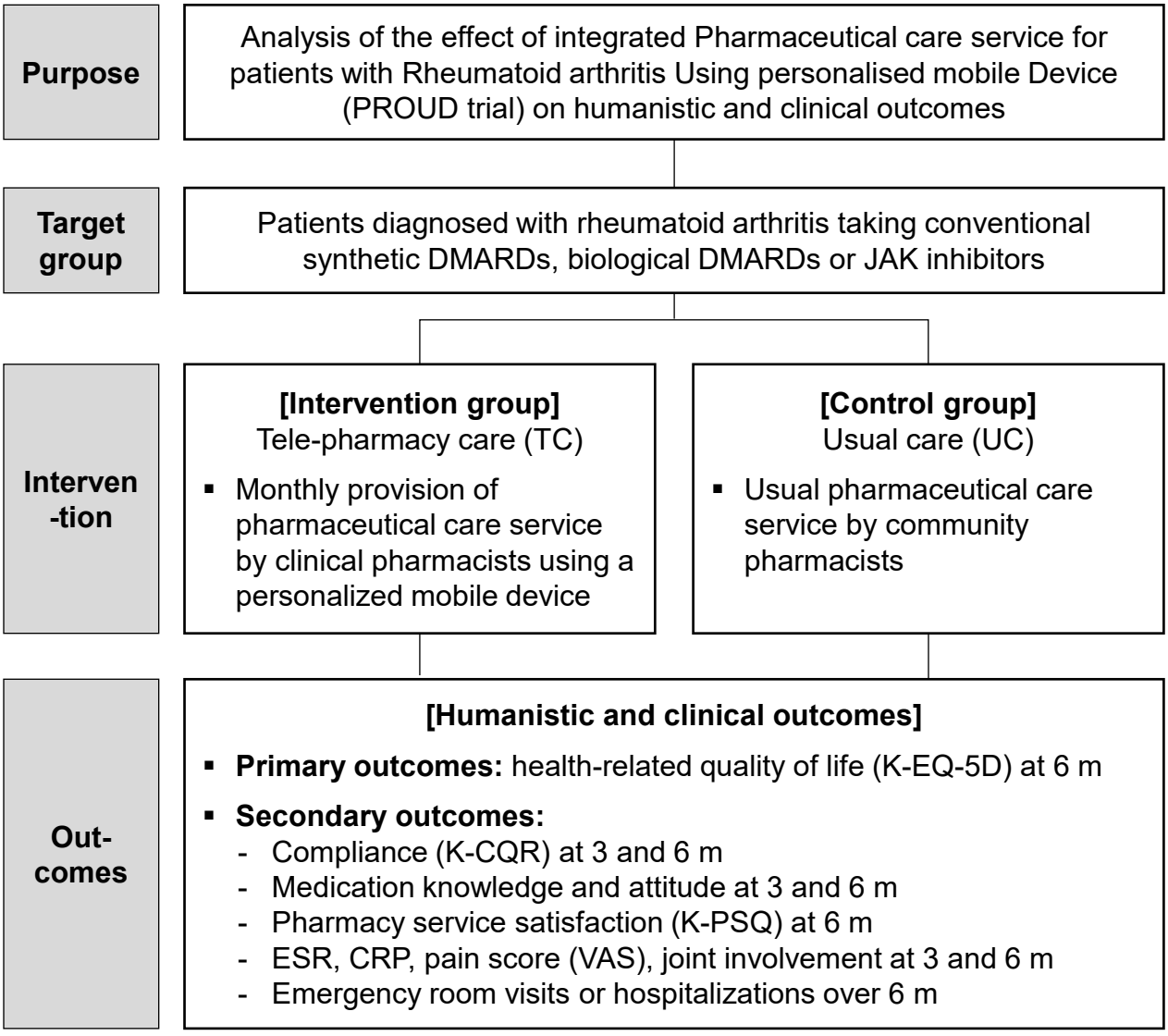
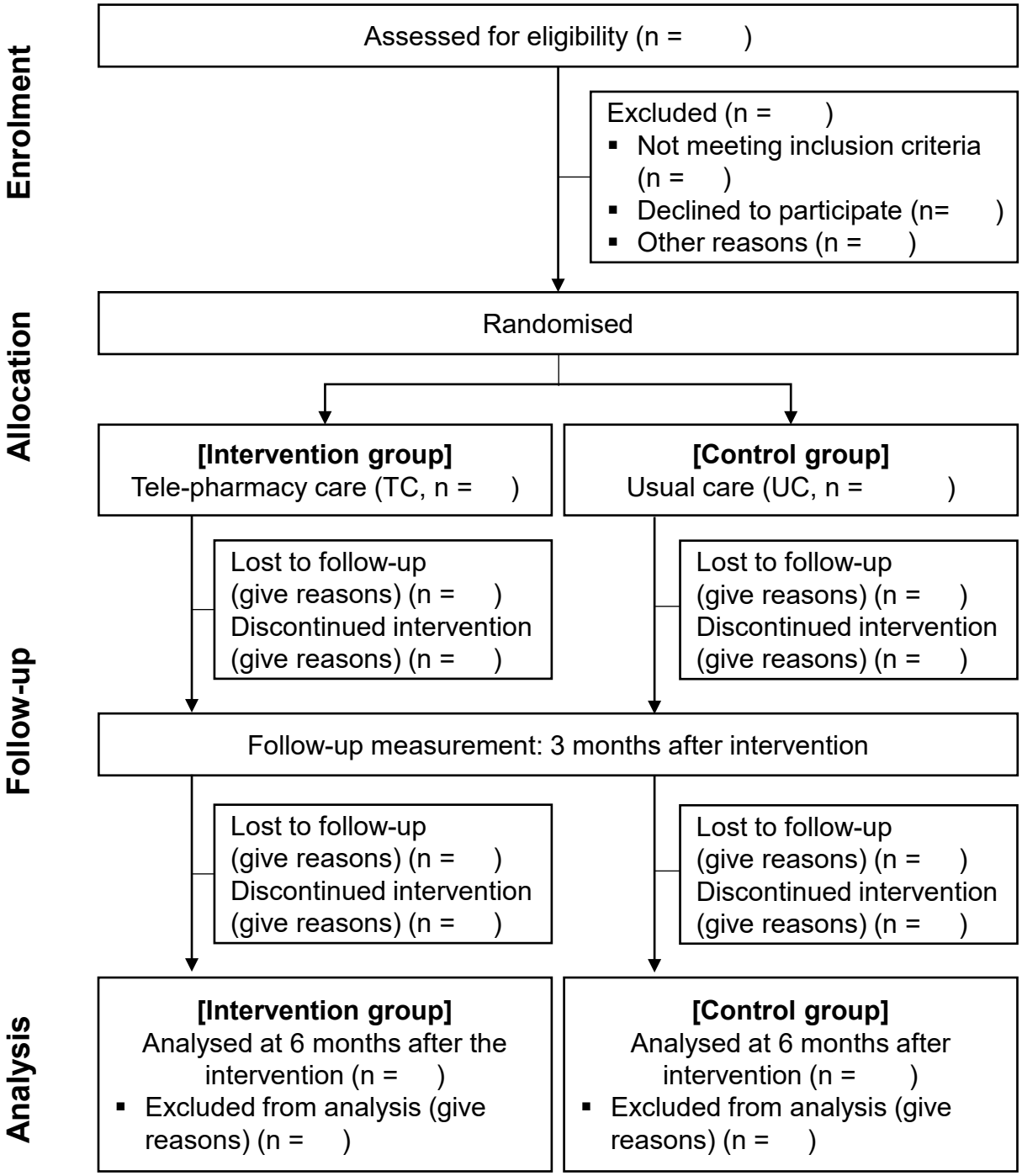
FIGURE LEGENDS

Figure 1. PROUD study design. Abbreviations: 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-5 dimension questionnaire; K-PSQ, Korean version of the patient satisfaction questionnaire; VAS, visual analogue scale.

Figure 2. Flow diagram of the study design

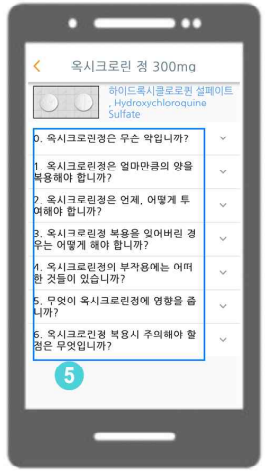
Figure 3. Patient's guide for an installation of a MediRA app, a personalised smartphone application for patients with rheumatoid arthritis


Purpose
Analysis of the effect of integrated Pharmaceutical care service for patients with Rheumatoid arthritis Using personalised mobile Device (PROUD trial) on humanistic and clinical outcomes
Target group
Patients diagnosed with rheumatoid arthritis taking conventional synthetic DMARDs, biological DMARDs or JAK inhibitors
Interven -tion
[Intervention group]
Tele-pharmacy care (TC)
Monthly provision of pharmaceutical care service by clinical pharmacists using a personalized mobile device
[Control group]
Usual care (UC)
Usual pharmaceutical care service by community pharmacists
Out- comes
[Humanistic and clinical outcomes]
Primary outcomes: health-related quality of life (K-EQ-5D) at 6 m
Secondary outcomes:
- Compliance (K-CQR) at 3 and 6 m
- Medication knowledge and attitude at 3 and 6 m
- Pharmacy service satisfaction (K-PSQ) at 6 m
- ESR, CRP, pain score (VAS), joint involvement at 3 and 6 m
- Emergency room visits or hospitalizations over 6 m


Enrolment
Assessed for eligibility (n =)
Excluded (n =)
Not meeting inclusion criteria (n =)
Declined to participate (n=)
Other reasons (n =)
Allocation
Randomised
[Intervention group]
Tele-pharmacy care (TC, n =)
[Control group]
Usual care (UC, n =)
Follow-up
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Follow-up measurement: 3 months after intervention
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Lost to follow-up (give reasons) (n =)
Discontinued intervention (give reasons) (n =)
Analysis
[Intervention group]
Analysed at 6 months after the intervention (n =)
Excluded from analysis (give reasons) (n =)
[Control group]
Analysed at 6 months after intervention (n =)
Excluded from analysis (give reasons) (n =)

MEDiRA

1 Enter 'Hospital Registration Number' in 'ID' to log in.



5 There is a detailed description of the medication you are taking.

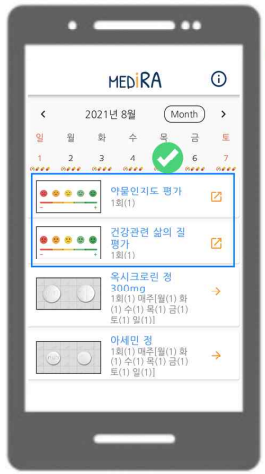
6 Click on each item to see the 'Detailed Description'.

7 If you press the ▶, you can listen to the detailed description 'Voice'.

2 Press for 1 week, 2 weeks, 4 weeks button. You can check a schedule.

3 If you select the date, you can check the number of medications, types of medications, and number of times taken on that day.

4 If you press ➡, you can check the ingredients, precautions, and how to take the medicine.



There have been surveys for 0, 3 and 6 months.

✔ When the screen appears, please click to answer the questionnaire.

(Version 2.1)

대상자 설명문

1. 연구과제명

류마티스관절질환자 대상 원격 모바일 약료서비스 성과분석 연구

2. 연구책임자

대구가톨릭대학교병원 류마티스내과 교수 김 지 원

3. 개요

이 연구는 비대면 서비스에 대한 사회적 요구도가 높은 상황에서, 전문 임상약사의 표준화된 원격 모바일 약사서비스 제공이 류마티스관절염 환자의 약물관리 효과에 미치는 영향을 평가하기 위한 연구입니다. 귀하는 류마티스관절염 치료를 위한 새로운 약물을 투여하기 시작하였기에 이 연구에 참여하도록 권유 받았습니다. 이 연구를 수행하는 대구가톨릭대학교병원 소속 연구책임자(김지원 교수) 혹은 연구담당자(박지은 약사, 070-8015-6040)가 귀하에게 이 연구 참여 과정에 대하여 설명해 줄 것입니다 이 연구는 자발적으로 참여 의사를 밝히신 분에 한하여 수행될 것이며, 귀하께서는 본 임상 연구에 참여 의사를 결정하기에 앞서, 본 임상연구가 왜 수행되고, 귀하의 정보가 어떻게 사용될지, 본 임상연구가 어떤 것을 포함하고 있는 지와 가능한 이점, 위험, 불편함은 무엇인지에 대하여 이해하는 것이 중요합니다. 다음의 설명을 신중하게 시간을 가지고 주의 깊게 읽으시기 바라며, 필요하시면 귀하의 주치의 또는 가족이나 친구들과 상의하시기 바랍니다. 만일 어떠한 질문 사항이 있으시면 연구자가 자세하게 설명해 줄 것입니다.

4. 연구의 목적 및 배경

관절 활막의 지속적인 염증 반응을 특징으로 하는 류마티스관절염은 일반적으로 관절 손상을 예방하고 골밀도를 보존하기 위해 장기적 약물치료가 필수적입니다. 약물의 치료효과를 높이고 합병증을 관리하기 위해 의사, 간호사 및 임상약사에 의한 통합적인 보건의료서비스에 대한 요구도가 높아졌습니다. 아울러, 최근 코로나 19 의 대규모 확산 사태와 함께 약물요법 관리를 위한 비대면 약사서비스 제공이 중요하게 고려되고 있습니다.

본 연구에서는 류마티스 관절염 환자에서의 효과적인 약물요법 관리를 위한 전문 임상약사의 표준화된 원격 모바일 약사서비스 제공이 질병 및 약물관리에 미치는 효과를 평가하고자 합니다.

5. 연구 약물/기기

본 임상시험은 비대면 약물사용교육 서비스가 중심이 되므로, 이 연구에 참여함으로써 귀하에게 새롭게 투여되는 약물이나 기기는 없습니다. 귀하가 본 임상연구에 참여하는 동안 류마티스관절염을 치료하기 위해 받게 되는 모든 약물요법 및 치료적 처치는 연구참여 여부와 상관없이 의학적 판단에 따라 이루어집니다.

(Version 2.1)

6. 대안 치료 (임상시험 이외의 다른 대체 가능한 치료법)

귀하가 본 연구에 참여하기를 원하지 않는다면, 귀하의 연구 담당의사는 귀하에게 적절한 치료법에 대해 설명할 수 있으며 귀하는 모든 표준 요법들로 치료받으실 수 있습니다.

7. 연구방법에 관한 설명

(1) 절차 또는 치료

본 연구에 참여한 대상자는 무작위배정을 거쳐 1:1 의 비율로 원격 모바일 약사서비스군(시험군)과 기존 약사서비스군(대조군)으로 나누어집니다. 두 군 모두 기존의 치료와 처치, 검사를 받게 되며, 시험군의 환자는 추가적으로 본 연구의 계획에 따라 원격 모바일 약사서비스를 제공받게 됩니다. 1 개월 간격으로 유선으로 약사가 귀하에게 전화를 할 것이며, 약사는 복용 중인 약물을 조사하고 복약상담과 복약순응도 향상을 위한 교육을 제공할 것입니다. 평상시에 귀하는 모바일 어플리케이션을 활용하여 환자별로 맞춤형으로 제공된 약물정보를 토대로 약물복용과 관련하여 궁금한 내용을 확인할 수 있으며, 삶의 질과 복약순응도는 설문으로 평가하게 됩니다.

방문일정	설문조사
방문 1 (외래 등록 시)	삶의 질, 복약순응도, 약물인지도, 환자만족도
방문 2 (연구시작 3 개월 ± 7 일 후)	복약순응도, 약물인지도
방문 3 (연구시작 6 개월 ± 7 일 후)	삶의 질, 복약순응도, 약물인지도, 환자만족도

(2) 연구기간 및 대상자 참여 기간, 예상 대상자 수(전체 대상자 수/본원 대상자 수)

본 임상연구는 대구가톨릭대학교병원 생명윤리위원회의 승인일로부터 2023.12.31.까지 진행됩니다. 본 임상연구에 참여하는 대략의 대상자 수는 256 명으로 각 대상자의 연구참여 예상기간은 무작위배정 이후 최소 6 개월입니다.

(3) 시험 제한 사항 및 대상자 의무

본 연구에 참여하는 동안 본 기관에서 처방하는 약물 또는 관리 외에 별도의 다른 약물을 사용(복용하거나, 주사로 투여하거나, 피부에 바르는 등)할 경우에는 반드시 연구담당자에게 알려주십시오. 연구담당자의 지시에 따르지 않거나, 추적관찰에 실패할 경우 귀하는 귀하의 동의 없이도 본 연구의 참여로부터 제한될 수 있습니다.

(4) 대상자 선정, 제외기준

- **대상자 선정기준**

① 대구가톨릭대학병원 류마티스내과를 방문하는 18 세 이상 외래 환자 중 류마티스 관절염으로 진단받고 다음과 같은 DMARD 를 1 개 이상 투여하는 자

- Conventional DMARDs: Hydroxychloroquine, methotrexate, sulfasalazine, bucillamine, leflunomide
- 생물학적 DMARDs (피하주사제): etanercept, adalimumab, golimumab
- JAK 억제제: tofacitinib, baricitinb

② 무작위배정 시점에 새로운 약물(DMARD, 스테로이드제, 또는 진통제)를 투여하기 시작한 자
③ 모바일 기기(스마트폰 등)을 소지한 자
④ 연구 참여에 동의한 자

- **대상자 제외기준**

① 인지능력 저하 등으로 인해 서면 또는 면접설문 응답이 어려운 환자
② 중증의 전신 또는 악성 질환자 (ECOG 2점 이상, 악성 종양을 진단받고 치료 중인 자)
③ 모바일 기기에 복약순응도 향상도구(동 연구에서 제작한 별도의 어플리케이션 또는 앱)이 설치되지 않거나 설치에 동의하지 않는 자
④ 멀티미디어 메시지 서비스(Multimedia Messaging Service, MMS)를 이용한 복약정보 제공에 동의하지 않는 자
⑤ 기타 연구진이 연구 참여에 적절하지 않다고 판단한 자

8. 대상자에게 예견되는 이상반응, 위험과 불편함

본 연구는 비대면 약물사용교육 서비스가 중심이므로 참여하는 대상자에게서 연구 수행 시 진행되는 모든 검사나 교육은 침습적이거나 위험하지 않습니다. 따라서 본 연구 참여로 인해 나타날 것으로 예상되는 추가적인 부작용이나 불편은 없습니다. 단, 본 연구에의 참여로 인해 받게 되는 복약상담 및 교육서비스에 다소간의 시간이 소요될 수 있습니다

9. 대상자에게 예견되는 이득

귀하가 본 연구에 참여함으로써 귀하에게 의학적 혜택이 보장되는 것은 아닙니다. 본 연구에 참여하는 동안 받게 되는 모든 약물요법 및 치료적 처치는 연구참여 여부와 상관없이 동일합니다. 그러나, 전문임상약사에 의해 추가적인 비대면 약물사용교육 서비스를 제공받음으로써 효과적인 약물요법 관리가 가능하고 약물의 효과를 높일 수 있을 것으로 기대됩니다.

10. 연구 관련 새로운 정보의 지속적 제공

본 연구 기간 중 귀하의 시험 참여 여부를 결정하는데 영향을 줄 수 있는 새로운 유의한 정보가 얻게 되는 즉시 귀하 또는 귀하의 대리인에게 알려 드릴 것입니다.

11. 금전적 지급

본 연구 참여 중 실시되는 모든 약물요법 및 검사 과정은 연구에 참여하지 않더라도 받아야 하는 것으로 약제 및 검사비에 대한 보상은 없으며 연구에 참여함으로써 대상자에게 추가적으로 발생하는 별도의 비용은 없습니다. 본 연구의 참여로 인해 소요되는 시간에 대한 보상으로 첫 방문과 연구시작 6 개월째 마지막 방문 시 각각 1 만원의 교통비가 지급될 예정입니다.

12. 피해발생 시 대상자 보상(의료적 치료/보상)

본 연구는 기존 진료에서 진행되고 있는 시술 또는 치료 방법(의약품, 의료기기 포함)에 추가로 약사에 의한 비대면 약물요법관리가 이루어지는 연구로서, 의학적으로 판단하였을 때 동 연구로 인한 추가적 위험이 기존 진료 과정에서 진행되고 있는 시술 또는 치료 방법보다 현저하지 않습니다. 따라서 이 연구로 인해 대상자가 추가적으로 입게 되는 신체적, 정신적 위해 및 특이 손상은 없을 것으로 예측됩니다. 대상자들에게는 통상적인 진료 과정에서 이루어지는 안전 보호 대책이 적용될 것이며, 연구 시작 전 연구대상자들에게 해당 연구의 목적과 방법 등에 대해 충분한 정보가 제공될 것입니다.

13. 비밀 보장

연구대상자의 신원을 파악할 수 있는 기록은 비밀로 보장될 것이며, 연구의 결과가 출판될 경우 연구대상자의 신원은 비밀상태로 유지될 것입니다. 연구대상자 번호는 환자의 병원등록번호가 아닌 각 환자마다 임의의 번호를 할당하여 관리할 것이며, 연구를 위해 수집되는 모든 정보와 자료는 잠금장치가 있는 연구책임자가 지정한 곳에 보관할 것입니다. 연구관련 기록은 연구완료시점부터 3 년간 보관하며, 보관기간이 지난 문서나 파일은 개인정보보호법에 따라 파기할 것입니다.

14. 의무기록의 열람

임상연구의 책임연구자, 연구담당자, 공동연구자, 생명윤리위원회(IRB)는 관계 법령에 따라 연구의 절차와 자료의 품질을 검증하기 위하여 대상자의 신상에 관한 비밀이 보호되는 범위에서 대상자의 연구기록을 열람할 수 있습니다. 대상자 또는 대상자의 대리인이 서명한 동의서에 의하여 이러한 자료의 열람이 허용될 것입니다.

15. 자발적 참여

본 연구에 참여하시는 것은 귀하에게 달려 있습니다. 귀하는 언제든지 시험에 참여하지 않기로 결정할 수 있고 또한 시험을 그만 둘 수 있습니다. 귀하가 본 연구에 참여하지 않아도 아무런 불이익을 받지 않으며 귀하의 결정은 향후 귀하가 진료를 받는 것에 영향을 미치지 않습니다.

16. 연구의 중지

연구담당 약사의 지시를 따르지 않거나, 정해진 기간에 유선을 통한 연락이 되지 않아 추적관찰에 실패한 경우, 연구자의 판단 하에 더 이상 연구 참여가 부적합한 경우(예: 인지능력 상실 등)에 귀하는 귀하의 동의 없이 본 연구의 참여가 제한될 수 있습니다.

17. 개인정보 제공에 관한 사항

본 동의서에 서명함으로써 귀하는 연구진이 귀하의 개인정보 및 민감정보를 수집하고 사용하는데 동의하게 됩니다.

- **개인 및 민감정보의 수집·이용 목적**

  개인정보: 귀하의 이름, 주소, 휴대전화번호, 출생연도, 성별, 이메일주소

  민감정보: 류마티스관절염 유병기간 및 약물복용기간, 동반질환, 흡연력, 키, 체중, 혈압, 맥박수, 임상검사정보, 응급실 방문 또는 입원 정보, 설문조사 정보(건강관련 삶의 질, 복약순응도, 약물인지도, 약사서비스만족도 등), 모바일 기기 정보(이동통신사 정보, 단말기 정보), 쿠키, 접속기록, 접속시간

  수집·이용 목적: 귀하의 성명, 성별, 나이, 병원등록번호, 임상연구 과정에서 발생하는 진료기록 및 자료 등 건강 관련 정보는 연구 관련 임상 정보의 획득 및 확인을 위한 목적으로만 수집되며 이용됩니다.

- **개인 및 민감정보의 보유 및 이용 기간**

  귀하의 개인 및 민감정보는 연구를 위해서만 사용되며 수집된 개인정보는 개인정보 보호법에 따라 적절히 관리됩니다. 수집된 개인정보 및 민감정보는 연구 결과보고 후 3 년간 보관 후 폐기합니다.

- **동의를 거부할 권리가 있다는 사실 및 동의 거부에 따른 불이익이 있는 경우에는 그 불이익의 내용**

  귀하는 위 개인 및 민감정보 수집 및 이용, 제공에 대한 수락 여부를 자유롭게 결정할 수 있습니다. 귀하가 개인 및 민감정보 수집 및 이용, 제공에 수락하지 않는 경우에도 귀하에 대한 진료와 처방에 어떠한 불이익도 발생하지 않습니다.

18. 연구 관련 책임자 및 연락처

귀하는 연구책임자 혹은 연구담당자(박지은 약사/070-8015-6040)에게 임상연구 기간 중에 언제든지 추가적인 정보를 요청할 수 있습니다. 또한 귀하는 연구 대상자로서의 귀하의 권리에 대해 의문이 있을 경우 대구가톨릭대학교병원 생명윤리위원회(053-650-3062, 3063)로 연락할 수 있습니다.

(Version 2.0)

대상자 동의서

연구과제명: 류마티스관절질환자 대상 원격 모바일 약료서비스 성과분석 연구

1. 본인은 임상연구에 대해 구두로 설명을 받고 상기 대상자 설명문을 읽었으며 담당연구원과 이에 대하여 의논하였습니다.
2. 본인은 위험과 이득에 관하여 들었으며 나의 질문에 만족할 만한 답변을 얻었습니다.
3. 본인은 이 연구에 참여하는 것에 대하여 자발적으로 동의합니다.
4. 본인은 이후의 치료에 영향을 받지 않고 언제든지 연구의 참여를 거부하거나 연구의 참여를 중도에 철회할 수 있고 이러한 결정이 나에게 어떠한 해가 되지 않을 것이라는 것을 알고 있습니다.
5. 본인은 이 설명서 및 동의서에 서명함으로써 의학 연구 목적으로 나의 개인정보가 현행 법률과 규정이 허용하는 범위 내에서 연구자가 수집하고 처리하는데 동의합니다.
6. 본인은 개인정보 및 민감정보의 수집, 이용에 대한 설명을 이해하고 이에 동의합니다.

본인은 본 연구의 수행에 따른 개인정보의 수집 및 이용에 동의합니다.	예□ 아니오□
본인은 본 연구의 수행에 따른 민감정보의 수집 및 이용에 동의합니다.	예□ 아니오□

7. 본인은 이 동의서 사본을 받을 것을 알고 있습니다.

대상자 성명	서명	날짜 (년/월/일)
법정대리인 성명 (대상자와의 관계:)	서명	날짜 (년/월/일)
입회인 성명 (해당되는 경우)	서명	날짜 (년/월/일)
성명 연구책임자 또는 연구책임자의 위임을 받은자	서명	날짜 (년/월/일) * 대리인이 서명하는 경우 대리인임을 확인 할 수 있는 서류 첨부

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2, 19

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#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	NA
Roles and responsibilities: committees	#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)	NA

Introduction

Background and rationale	#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	5–6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5–6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#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	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	6–7

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8–12
Interventions: modifications	#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)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8–9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#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	12–13
Participant timeline	#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)	14–16

Sample size	#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	17
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7–8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#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	8
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	NA
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7–8

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#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	12-17
Data collection plan: retention	#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	8-12, 18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	16-17

		(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	
Statistics: outcomes	#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	18-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis population and missing data	#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)	18
Methods: Monitoring			
Data monitoring: formal committee	#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	NA
Data monitoring: interim analysis	#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	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing	8-9

		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	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
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)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	16-17

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-17
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	18
Dissemination policy: trial results	#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	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	NA

biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable