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Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: protocol for a randomized controlled clinical trial

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Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: protocol for a randomized controlled clinical trial

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Abstract

Introduction: The WOMAC index is the most commonly used indicator of disease-specific outcome in knee osteoarthritis for its convenience and reliability. It has two formats the paper-based WOMAC (p-WOMAC) and the electronic WOMAC (e-WOMAC). In China, the p-WOMAC has been widely used though e-WOMAC is yet untested. This study aims to test whether e-WOMAC is consistent with the p-WOMAC before and after the intervention.

Methods and analysis: A total of 240 patients from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine will be randomly assigned in two groups named group A and group B. This study is divided into three stages. In the first stage, patients in group A will be evaluated first by p-WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC and then by p-WOMAC. In the second stage of the study, drug interventions will be implemented. 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. In the third stage, post-intervention evaluation will be conducted after administration. Patients in group A will be evaluated first by e-WOMAC and then by p-WOMAC. Patients in group B will be evaluated first by p-WOMAC and then by e-WOMAC. In order to avoid the possible bias because of patients' potential memory, e-WOMAC and p-WOMAC will be taken for each patient at 15 minutes apart. The primary outcome of the study is the mean score difference in WOMAC, and the secondary outcomes are the score differences in WOMAC subscales: pain, stiffness, and physical function.

Ethics and dissemination: The protocol has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01). The results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: ChiCTR2100050914

Strengths and limitations of this study

This is the first study to evaluate the impact of Chinese WOMAC index in normal clinical practice in a Chinese population.

It is an effectiveness-implementation hybrid trial that aims to promote more effective and patient-centred care of people with KOA.

Utilizing modern technology, this study seeks to overcome implementation barriers by gathering and analyzing WOMAC index as related to the general population to produce a patient-filled report.

Based on the results of this study, routine WOMAC data collection can be integrated into electronic medical records if it is effective.

As the instruments will be collected using electronic tablets, a certain level of computer literacy is required, and the study may not be able to include participants who are not capable of handling the devices

Introduction

Knee osteoarthritis (KOA) is the most common chronic, progressive and degenerative joint disease in middle and old age. It is characterized by articular cartilage degeneration, osteosclerosis and hyperplasia. Major clinical manifestations of KOA include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the lower limb and affect patients' normal life and work. [1] In China, approximately 3% of Chinese people are affected by OA, mostly KOA. There is radiographic evidence of knee osteoarthritis in up to 60% of middle-aged population. People over 65 years old even have a 25% higher incidence rate. KOA can greatly affect the patients' health and quality of life. Today, its incidence tends to increase with the advent of an aging society. [2-3] With increased demand for health, people are becoming more aware of the need for early diagnosis, timely intervention, minimal damage and better prognosis. Patient-reported outcomes (PRO) can truly reflect patients' health status and treatment outcomes, and have played a significant part in diagnosis and treatment for chronic

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progressive diseases. The WOMAC is a specific PRO scale, which has high reliability and sensitivity for KOA severity assessment and can accurately reflect the patients' symptoms and functional limitations, while having little influence on the subjective tendency of the patients.[4] For those who have mild symptoms of OA, it shows high reliability and is currently the most widely used tool to assess severity level of KOA.[5]

Although the paper-based WOMAC has already been accepted and widely used, there are still several shortcomings such as difficulties of collecting and analyzing pen-and-paper based data. Especially when it comes to the quality of clinical research, traditional paper-based data is hard to be accessed retrospectively. In times of IT and communication technologies, smartphone application provides technical basis for online assessment and telemedicine.[6-8] Nowadays, many different forms of WOMAC on the mobile phone, tablet or pc are emerged in large numbers, namely electronic WOMAC (e-WOMAC) which have been favored by researchers and become the first choice of assessment of KOA in the clinical practice and research.

The visual analogue scale (VAS) is used in e-WOMAC for assessment of KOA. Pain, stiffness and dysfunction assessment can be completed directly at any time at home through e-WOMAC application and then physicians can rapidly understand patient's condition and adapt treatment to achieve personalized healthcare by telemedicine. [9] The main advantages of the e-WOMAC include high efficiency, lower data collection error rate, shorter response time and increased response rates. [10-13] Practically, online medical service is potentially beneficial for patients with KOA: electronic questionnaire can be completed almost anytime and anyplace alleviating the influence of environmental factors. The online medical models of care also protect the patients' privacy and avoid multiple visits to the clinic. Additionally, paper-less records reduce the waste of resources, which is beneficial for the environment.

Before being put into use, many countries including the UK, Australia, Switzerland and Austria have demonstrated the reliability of the e-WOMAC. R.Theiler argues that English e-WOMAC has similar responsiveness in detecting clinically

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meaningful change than the traditional p-WOMAC. [14] HA Bischoff-Ferrari makes a similar point in his study of consistency between German e-WOMAC with the original format as well. [15] Similarly, R.Theiler found that the Swiss computerized WOMAC 3.1 and conventional p-WOMAC are similar in all three subscale. [16] Overall, these studies illustrate the heterogeneity that electronic data capture (EDC) is a promising alternative to traditional paper-based mode.

In China, the existing body of research on the Chinese paper-based WOMAC numerical rating scale (NRS) 3.1 suggests its psychological robustness in reliability and validity. [17] The research also shows that compared with Lysholm score, IKDC score, HSS score, KSS score and other scale used in assessment of KOA, Chinese WOMAC 3.1 is the most suitable assessment scale. However, the Chinese electronic WOMAC hasn't been put into use, so research to date has not yet determined the equivalence of Chinese e-WOMAC and the traditional p-WOMAC.

Objective

By this research, we aim to provide conclusive evidence for developing patient-centered online health application. We hypothesize that the equivalent between two formats of the WOMAC will be proved, then our study objectives is to assess: 1.The comparability of results generated from these two WOMACs. 2.Subjects' acceptance and satisfaction with the Chinese e-WOMAC index.

Method

Study design

This study is a randomised controlled trial (RCT) aims to evaluate the consistency between the Chinese electronic WOMAC (e-WOMAC) and paper WOMAC (p-WOMAC) evaluations of patients with knee osteoarthritis (KOA). The study schedule of enrollment, interventions and assessments are shown in Table1.

Table 1 Study schedule of enrolment, interventions and assessments.

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STUDY PERIOD			
	Pre-intervention	**Intervention period**	**Close-out**
TIMEPOINT	**T_0** Pre-intervention	**T_1** Between assessments	**T_2** One month follow-up
ENROLMENT:			
Eligibility screen	√		
Informed consent	√		
Allocation	√		
INTERVENTION:			
Medical treatment		√	
P-WOMAC analysis	√		√
E-WOMAC analysis	√		√
ASSESSMENTS:			
Demographics	√		
Primary outcomes			
WOMAC total score	√		√
Secondary outcomes			
WOMAC pain score	√		√
WOMAC stiffness score	√		√
WOMAC function score	√		√

Recruitment and Randomization

A total of 240 patients with KOA will be recruited from the Orthopedic Clinic of Shuguang Hospital affiliated to SHUTCM. The KOA patient will receive a clinical examination by an orthopedic surgeon. Patients with KOA meeting the inclusion criteria will be given the detailed information of this study. The importance of patients' active participation in the study and self-monitoring of the disease will be emphasized

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to improve their enthusiasm. All participants will be provided with an information sheet and sign the informed consent. After participation acceptance, the patients will be divided into two groups by randomly generated computer numbers, 120 patients in each group. Neither the researchers nor the patients will be blinded to the evaluation and treatment assignment.

Figure.1 provides an overview of the flow of study. The study is divided into three stages. In the first stage (T0) patients in group A will be evaluated first by p-WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC and then by p-WOMAC. In the second stage of the study, drug interventions will be implemented. 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. The third stage is the consistency evaluation stage after intervention. The post-intervention evaluation will be conducted after administration on day 21 (T2). Patients in group A will be evaluated first by e-WOMAC and then by paper WOMAC. Patients in group B will be evaluated first by p-WOMAC and then by e-WOMAC. In order to eliminate the possible bias because of patients' potential memory, e-WOMAC and p-WOMAC evaluation will be taken for each patient at 15 minutes apart in the first and third stage. This study has been registered in Chinese Clinical Trial Registry (ChiCTR2100050914) and will be conducted in strict accordance with Chinese ethical laws and regulations.

Blinding

Because of the nature of the study protocol, blinding method will not be used in this study. The data collection and analysis will be carried out by a single researcher who is not aware of the study grouping and intervention arrangements.

Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) patients who meet the KOA diagnostic criteria of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint Surgery Group of the Orthopaedic Society of the Chinese Medical Association; (2) patients aged 40 to 70 years, including 40 and 70 years, male or female; (3) KL

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classification≤ grade 3; (4) patients who have a mobile phone and can use the application proficiently; (5) patients who understand Chinese language and can complete the WOMAC independently; (6) patients who have signed the informed consent.

Exclusion criteria are as follows: (1) patients with acute meniscus injury, peripheral ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of knee joint, tuberculosis, idiopathic osteonecrosis of the knee; (2) patients with serious cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other hemorrhagic diseases, mental illness, pregnancy and lactation; (3) patients who are allergic or intolerant to trial medication; (4) Patients who had received other treatments in the last 2 months has an effect on the study; (5) patients who are deemed unsuitable for the clinical trial.

Sample size calculation

There is no previous literature report and the sample size calculation will not be applicable to this study.

Instrument

WOMAC is a widely used self-administered evaluation tool, which can be completed within 5-10 minutes. Research shows that this scale has objective reliability, effectiveness and sensitivity for evaluation of the knee joint, and it is an evaluation scale that has been widely used for patients with OA. The WOMAC rating scale assesses the structure and function of the hip and knee in terms of pain, stiffness, and joint function. There are 24 items in all covering the basic symptoms and signs of OA, 5 items for the pain part, 2 items for the stiffness part, and 17 items for the joint function part, among which each item has a scale bar without scale line, representing the range of 0-10 points, the starting point on the left side of the scale is 0 point, representing none, and the end point on the right side is 10 points, representing extreme severity. [18] The regular paper-based WOMAC requires the patient to fill out based on his or her symptoms and signs within 48 hours, which is then measured by a physician based on

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the location. E-WOMAC, a Chinese-language electronic scale for self-assessment of patients with KOA, used in the study was developed by Shanghai Jsure Health Co. The text portion of e-WOMAC is identical to WOMAC VAS 3.1. For the first time, the patient needs to scan the QR code and download the Epdata software. After registration and login, patients can fill in the electronic version of WOMAC (figure.2), swipe the ruler on the screen according to their symptoms and signs within 48 hours, and submit after completing the answers. Doctors can directly receive the score data of patients in the Epdata database (figure.3).

Additional Questions

In the end of the study, a simple questionnaire has been designed to investigate subjects' perceptions of the study and the propensity for paper-based or electronic version of WOMAC. The questions will involve the description of the advantages and disadvantages of two WOMACs.

Interventions

Other medications and treatments for KOA, including oral medications, topical plasters, acupuncture, acupotomy, and arthroscopy will not be available during the study period. If the patient needs additional treatment, they need to contact the doctor in advance. To increase the participation of the patients, we make sure all the treatment of the subjects during the study is free of charge, and the subjects in the trial can have X-ray and MRI images free of charge and receive appropriate transportation subsidy. The investigator will make every effort to prevent and treat any harm that may result from this study. If adverse events occur in the clinical trial, a committee of medical experts will determine whether it is associated with the treatment. The sponsor will provide the cost of treatment and the corresponding financial compensation for the damage related to the trial in accordance with the Provisions of China's "Standard of Quality Management of Clinical Trials for Drugs".

Primary outcomes

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The primary outcome of the current study is the mean score difference in WOMAC. This method has been found to be a semi-quantitative rating scale with better reliability and validity and more balanced empirical evidence. [18] The Chinese e-WOMAC which contains 24 different items split up into 3 subscales: pain subscale (5 items), stiffness subscale (2 items) and physical function subscale (17 items) will be asked to patients. Primary outcomes will be analyzed and reported in two ways. First, we will compare the difference in the respective score of e-WOMAC and p-WOMAC before and after the intervention. Then, we will investigate patients' acceptance of two forms of the WOMAC through a simple self-made questionnaire.

Secondary outcome

Additionally, the secondary outcomes include the WOMAC VAS 3.1 Pain Scale (ranging from 0 (no pain during movement) to 500 (extreme pain during movement)), the WOMAC Stiffness Scale (ranging from 0 to 200 with higher scores meaning more severe limitation) and the WOMAC Physical Function Scale (ranging from 0 to 1700, with higher scores indicating more serious impairment during activities). The secondary outcome analyses will be assessed similarly to the main endpoint analyses.

Data collection and management

We will try to collect resulting data from all patients in the study, including those who never attend or discontinue therapy, those who discontinue participation in the study and those who get away. We will gather information at every stage of recruitment, randomization and treatment so that we can report flow of patients according to the CONSORT guidelines.

The paper questionnaire will be completed by subjects alone and data will be collected by trained investigators, then reached the database. The electronic questionnaire will be completed by subjects alone via the smartphone application. The score of e-WOMAC will be entered into an excel file and then analyzed by SPSS. Note that time intervals between two assessments should be 15 minutes in order to eliminate

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the influence of memory and maintain data quality and objectivity.

Statistical analysis

The aim of the study is to describe a randomized trial designed to test the effectiveness and reliability of mobile phone application for assessment of KOA compared with traditional mode of pen-and-paper based, episodic, onsite evaluation. As the average scores of the two versions of the outcome measures are the same, there may also be significant differences in the scores of individual respondents, and/or differences on certain items. The total score and each dimension of e-WOMAC and p-WOMAC will be separately analyzed. All data analysis will be performed by SPSS17.0 statistics software, mean ± standard deviation (SD) is used to described the metrological data following the normal distribution while median (M) and interquartile range (Q) are used to described the data not following the normal distribution.

First, two conditions will be compared at baseline with a between-group analysis via a t-test in order to ensure there is no difference between randomization groups. To test our hypothesis, in the first stage calculate difference scores of each participant (difference d = paper WOMAC total score - electronic WOMAC total score) and the data will be analyzed for normality by the Shapiro-Wilks test. A paired t-test will be used to calculate the mean score difference if data is normally distributed, and the results will be reported as 95% confidence intervals between differences in means, if not, Wilcoxon rank-sum test will be used. Two factor ANOVA model will be used to account for any differences due to the order of completing the paper and electronic WOMAC index. In the third stage, the same statistical analysis will be performed after the intervention the same as the first stage in order to investigate whether the WOMAC score of both high and low levels of KOA has good consistency.

To test the consistency of two versions of the WOMAC, an allowed range is defined (i.e. a value for the mean difference that needed to be exceeded to determine that the two WOMACs are not equivalent). As there is great inter-individual variability

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between different patients, a limit of equivalence will be determined based on the outcome measure of the pre-experiment to provide a strict test of the equivalence of two WOMACs. If the mean (and its 95% confidence interval) of the difference falls within the allowable ranges, then we can gain the credible evidence of equivalence of scoring system of the WOMAC.

Answers to open-ended questions will be subjected to a simple content analysis, categorized as positive, negative, or neutral comments on the e-WOMAC or p-WOMAC.

For the condition of shedding samples that may occur in the current study, we will have strict criterion and the statistical analysis will only include patients who participate in the whole process of the study from enrollment to post-intervention assessment. Moreover, we need them to record their medication-taking behavior in time so as to improve their adherence to the study which helps minimize the error.

Data monitoring

An external data monitoring committee was not deemed to be necessary for this trial. Data will be monitored by the research team which includes clinicians, statisticians and information technology experts. This study is considered to be a low-risk trial where both the intervention and control groups will receive their usual medical care. The expected duration of the trial lasts only 1 month and the use of the application does not present with high risk, there won't be any stopping guidelines to terminate the trial nor interim analysis planned.

Patient and public involvement

This research is planned to be done without patient involvement. The patients will not be invited to comment on the study design or be consulted on developing patient-relevant outcomes. The future manuscript will not be edited by patients for readability or accuracy.

Discussion

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Since KOA is characterized by chronic progressive degeneration of articular cartilage, its assessment involves a complex process and requires an overall evaluation of the patients' condition for a better clinical outcome. However today in China, many residents don't have the access to family doctors, so they usually need to go to hospital for treatment. The inconvenience in visiting doctors may cause delay in treatment. Smartphone application for electronic data capture appears to be an innovative and promising alternative to the original assessment methods as smartphone application have already been proved to be accurate tools.

However, it would be unwise to consider transforming a traditional paper-based patient-reported outcomes measure to an electronic version for use in the clinical practice and research if the equivalence of the two versions hasn't been proved. In this study protocol, we describe an unblinded trial designed to test a newly developed technology-based KOA assessment consisting of a mobile phone application for patients, which is linked to the physicians. Specifically, we want to explore the reliability and comparability of electronic and paper versions of the WOMAC and whether EDC can help improve treatment adherence by meeting patients' preferences.

To the best of our knowledge, this is the first study to test the reliability of the Chinese electronic WOMAC for KOA assessment. If our hypothesis is confirmed, the findings will serve to demonstrate the equivalence of electronic and paper versions of WOMAC and patients' acceptance of Chinese e-WOMAC so that it can be implemented in clinical practice and research. Likewise, our results will further demonstrate the feasibility of e-health for the personalized KOA therapy. (i.e. timely adjustment of the treatment plan can be rapidly given patients based on self-reported ePRO with the help of smartphone application)

We anticipate that with the support of EDC, physicians will be able to receive timely feedback on patients' conditions, which will significantly improve the visiting rate and treatment rate due to the convenience of telemedicine and rapid response to unwanted events. Note that KOA is a common chronic disease in the elderly, the study will explore the feasibility of enabling the Chinese e-WOMAC for patients' long-term use.

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However, using EDC systems may still have some limitations. The degree of familiarity with the electronics is not entirely consistent between different population, especially considering the factors of age, social status and other general factors. For example, some patients who don't have communication vehicles or cannot permit proper use of the application may be excluded from online medical service. In addition, psychological factors may have a relevant influence on filling out the questionnaire leading to the condition that patients feel non-adapted, have difficulty in using the smartphone or even failed to complete the questionnaire. [19] Accordingly, we can make some necessary adjustments of the application. In sum, the results of the present investigation may help to find new ways of developing smartphone application and information and communication technology in the medical field.

Data management and oversight

In order to ensure protocol compliance, proper study management, and timely completion of study procedures, members of the research team from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine will take responsibility for the conduct of all research staff and study participants.

Protocol and registration

The trial is registered with the ChiCTR, ChiCTR2100050914. Registered on 8 Sep 2021, https://www.chictr.org.cn/showproj.aspx?proj=133521

Data storage security and patient confidentiality

Patients' medical records will be kept in the respective hospital, and physicians will document the findings of the study in it, allowing researchers and ethics committees to access the data. Personal information of patients will not be revealed in the results of this study, and we will try everything we can to protect patients' privacy and medical data within the Chinese law. According to medical research ethics, experimental data especially personal privacy information will not be allowed to be

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accessed and shared by the public, and will be limited to web-based databases to ensure that personal privacy information is not disclosed.

Ethics and dissemination

The protocol for this trial has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01). All participants will be required to sign an informed consent form before enrollment in this study. The model consent form and other related documentation given to participants can be provided upon request.

Abbreviations

KOA: Knee osteoarthritis; WOMAC: Western Ontario and McMaster Universities Arthritis Index; e-WOMAC: electronic version of the WOMAC; p-WOMAC: paper-based WOMAC; e-health: online medical system; PRO: patient-reported outcomes; EDC： electronic data capture; SGH: Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

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Authors’ contributions

YJZ and YZ are the co-first authors. YJZ, YZ, KQL and YLC interpreted data. YJZ was responsible for writing of report, literature search, and selection of relevant articles. FL was responsible for the technical service of e-WOMAC.

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Disclaimer

The funding organisation has not played any role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required

Availability of data and material

Data sharing is not available to the public as no datasets were generated during the current study.

Consent for publication

Not applicable.

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Figure Legend

Figure1: Flow chart of the study
Figure2: Examples of the web for the subjects
(a) the Chinese e-WOMAC app interface after login;
(b) location of knee osteoarthritis: The picture shows the assessed joint（‘您不舒服的地方’means where do you feel uncomfortable？‘左膝’means left knee;‘右膝’means right knee ;‘双膝’means both sides of knee);
(c) e-WOMAC assessment of pain intensity: The picture shows a question about the level of the pain up and down the stairs in the WOMAC pain subscale.(‘上楼梯或下楼梯’means go upstairs and downstairs. Then choose pain level according to your feelings, the right end of the scale bar means extreme pain and the left means no pain.)
Figure3: Examples of the web for the physician (a)details and operation of subjects’ data; (b)the score of each question; (c)total score as well as pain, stiffness and physical function subscale scores of e-WOMAC.

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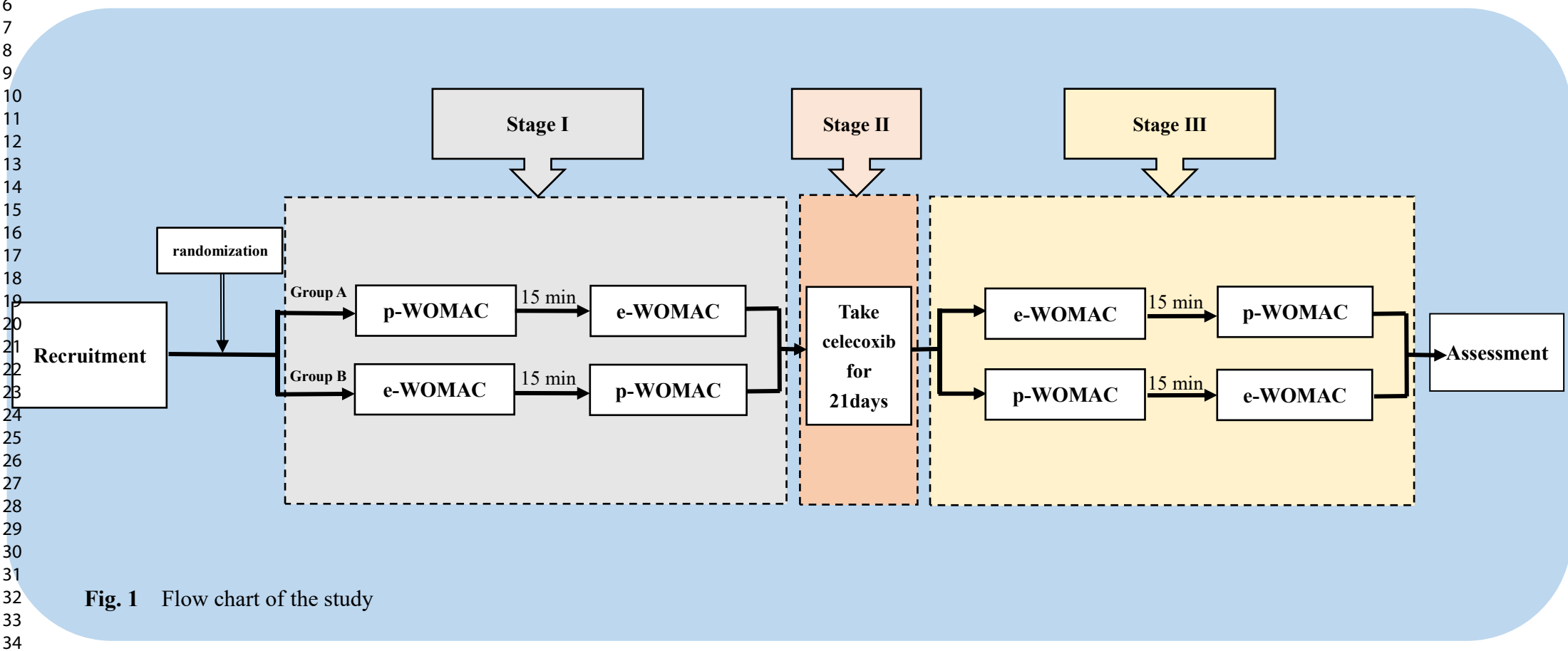

Fig. 1 Flow chart of the study

(a) (b) (c)

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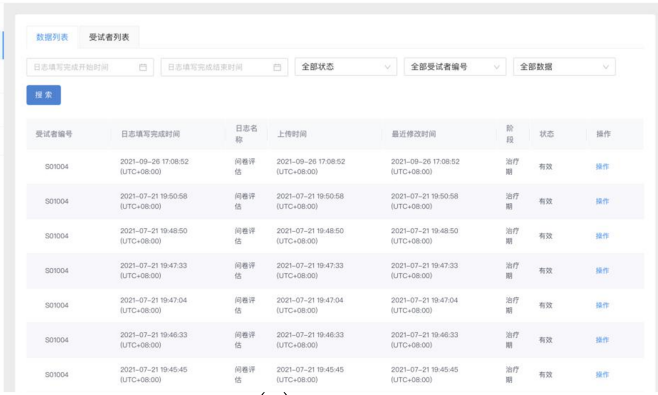

(a)

(b)

(c)

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Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: protocol for a randomized controlled clinical trial

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Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: protocol for a randomized controlled clinical trial

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Abstract

Introduction: The Western Ontario and McMaster University osteoarthritis index (WOMAC) is the most commonly used indicator of disease-specific outcome in knee osteoarthritis for its convenience and reliability. It has two formats the paper-based WOMAC (p-WOMAC) and the electronic WOMAC (e-WOMAC). In China, the p-WOMAC has been widely used though e-WOMAC is yet untested. This study aims to test whether e-WOMAC is consistent with the p-WOMAC before and after the intervention.

Methods and analysis: A total of 70 patients from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine will be randomly assigned in two groups named group A and group B. This study is divided into three stages. In the first stage, patients in group A will be evaluated first by p-WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC and then by p-WOMAC. In the second stage of the study, drug interventions will be implemented. 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. In the third stage, post-intervention evaluation will be conducted after administration. Patients in group A will be evaluated first by e-WOMAC and then by p-WOMAC. Patients in group B will be evaluated first by p-WOMAC and then by e-WOMAC. In order to avoid the possible bias because of patients' potential memory, e-WOMAC and p-WOMAC will be taken for each patient at 15 minutes apart. The primary outcome of the study is the mean score difference in WOMAC, and the secondary outcomes are the score differences in WOMAC subscales: pain, stiffness, and physical function.

Ethics and dissemination: The protocol has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01). The results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: ChiCTR2100050914

Protocol version: 1.0, 20 November 2021

Strengths and limitations of this study

This is the first study to evaluate the reliability and comparability of paper-based and Chinese electronic version of WOMAC index in normal clinical practice in a Chinese population.

Moreover, this trial focuses on subjects' propensity for paper-based or Chinese electronic version of WOMAC.

This study is a randomized, crossover design with intervention which can verify whether e-WOMAC is the same as p-WOMAC in sensitively reflecting the actual changes of patients' conditions.

As the instruments will be collected using electronic tablets, a certain level of computer literacy is required, and the study may not be able to include participants who are not capable of handling the devices.

Since the patients with KL classification ≤ grade 3 KOA were included in the study, the results will not be valid for severe KOA patients.

Introduction

Knee osteoarthritis (KOA) is the most common chronic, progressive and degenerative joint disease in middle and old age. It is characterized by articular cartilage degeneration, osteosclerosis and hyperplasia.[1] Major clinical manifestations of KOA include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the lower limb and affect patients' normal life and work.[2]

The worldwide prevalence of KOA is increasing, reported to be between 3.8% in 2010,and with an estimated 25,000 people suffer from KOA in 2018.[3] [4] There is radiographic evidence of knee osteoarthritis in up to 14% in asymptomatic uninjured adults aged <40 years and 43% of middle-aged population.[5] In China, approximately 8.1% of Chinese people are affected by KOA.[6] KOA can greatly affect the patients' health and quality of life. Today, its incidence tends to increase with the advent of an aging society.[7] With increased focus on health, people are becoming more aware of

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the need for early diagnosis, timely intervention, minimal damage and better prognosis. Patient-reported outcomes (PRO) can truly reflect patients' health status and treatment outcomes, and have played a significant part in diagnosis and treatment for chronic progressive diseases. The WOMAC is a specific PRO scale, which has high reliability and sensitivity for KOA severity assessment and can accurately reflect the patients' symptoms and functional limitations, and it is also less affected by subjective factors of the patients.[8] For those who have mild symptoms of OA, it shows high reliability and is currently the most widely used tool to assess severity level of KOA.[9]

Although the paper-based WOMAC has already been accepted and widely used, there are still several shortcomings such as difficulties of collecting and analyzing pen-and-paper based data. Especially when it comes to the quality of clinical research, traditional paper-based data is hard to be accessed retrospectively. In times of Information Technology and communication technologies, smartphone application provides technical basis for online assessment and telemedicine .[10] [11] [12] Meanwhile, a new mode of administration that patient-reported outcomes collected and recorded using electronic data capture(EDC) tool came into being and received increasing attention in recent years. Nowadays, many different forms of WOMAC on the mobile phone, tablet or pc appears in large numbers, namely electronic WOMAC (e-WOMAC) which have been favored by researchers and become a very useful tool for objective assessment of KOA in the clinical practice and research gradually.[13] [14]

The visual analogue scale (VAS) is used in e-WOMAC for assessment of KOA. Pain, stiffness and dysfunction assessment can be completed directly at any time at home through e-WOMAC application and then physicians can rapidly understand patient's condition and adapt treatment to achieve personalized healthcare by telemedicine. [15] The main advantages of the e-WOMAC include high efficiency, lower data collection error rate, faster response and increased response rates.[16] [17] [18] [19] Practically, online medical service is potentially beneficial for patients with KOA: electronic questionnaire can be completed almost anytime and anyplace alleviating the influence of environmental factors. The online medical models of care also avoid

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multiple visits to the clinic. Additionally, paper-less records reduce the waste of resources, which is beneficial for the environment.

Before being put into use, many countries including the UK, Australia, Switzerland and Austria have demonstrated the reliability of the e-WOMAC. R.Theiler argues that English e-WOMAC has similar responsiveness in detecting clinically meaningful change than the traditional p-WOMAC.[20] HA Bischoff-Ferrari makes a similar point in his study of consistency between German e-WOMAC with the original format as well.[21] Similarly, R.Theiler found that the Swiss computerized WOMAC 3.1 and conventional p-WOMAC are similar in all three subscale.[22] Overall, these studies illustrate the heterogeneity that the new mode of administration is a promising alternative to traditional mode.

In China, the existing body of research on the Chinese paper-based WOMAC numerical rating scale (NRS) 3.1 suggests its psychological robustness in reliability and validity.[23] The research also shows that compared with Lysholm score, IKDC score, HSS score, KSS score and other scale used in assessment of KOA, Chinese WOMAC 3.1 is the most suitable assessment scale. However, the Chinese electronic WOMAC hasn't been put into use, so research to date has not yet determined the equivalence of Chinese e-WOMAC and the traditional p-WOMAC.

Objective

By this research, we aim to evaluate the new mode of administration and provide conclusive evidence for developing patient-centered online health application. We hypothesize that the equivalent between two formats of the WOMAC will be proved, then our study objectives is to assess: 1. The comparability of results generated from these two WOMACs. 2. Subjects' acceptance and satisfaction with the Chinese e-WOMAC index.

Method

Study design

This study is a randomized controlled trial (RCT) aims to evaluate the consistency

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between the Chinese electronic WOMAC (e-WOMAC) and paper WOMAC (p-WOMAC) evaluations of patients with knee osteoarthritis (KOA). The study schedule of enrollment, interventions and assessments are shown in Table1. The start and end of the study was planned for September 2021 and December 2023, respectively.

Table 1 Study schedule of enrolment, interventions and assessments.

STUDY PERIOD			
	Pre-intervention	**Intervention period**	**Close-out**
TIMEPOINT	**T_0** Pre-intervention	**T_1** Between assessments	**T_2** One month follow-up
ENROLMENT:			
Eligibility screen	√		
Informed consent	√		
Allocation	√		
INTERVENTION:			
Medical treatment		√	
P-WOMAC analysis	√		√
E-WOMAC analysis	√		√
ASSESSMENTS:			
Demographics	√		
Primary outcomes			
WOMAC total score	√		√
Secondary outcomes			
WOMAC pain score	√		√
WOMAC stiffness score	√		√
WOMAC function score	√		√

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Recruitment and Randomization

A total of 70 patients with KOA will be recruited from the Orthopedic Clinic of Shuguang Hospital affiliated to SHUTCM. The KOA patient will receive a clinical examination by an orthopedic surgeon. Patients with KOA meeting the inclusion criteria will be given the detailed information of this study. The importance of patients' active participation in the study and self-monitoring of the disease will be emphasized to improve their enthusiasm. All participants will be provided with an information sheet and sign the informed consent by research nurse. After participation acceptance, the patients will be divided into group A and group B by randomly generated computer numbers, 35 patients in each group. Researcher not involved in patient care will prepare and administer the randomization schedule. Neither the researchers nor the patients will be blinded to the evaluation and treatment assignment.

Figure.1 provides an overview of the flow of study. The study is divided into three stages. In the first stage (T0) patients in group A will be evaluated first by p-WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC and then by p-WOMAC. In the second stage of the study, drug interventions will be implemented. 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. The third stage is the consistency evaluation stage after intervention. The post-intervention evaluation will be conducted after administration on day 21 (T2). Patients in group A will be evaluated first by e-WOMAC and then by paper WOMAC. Patients in group B will be evaluated first by p-WOMAC and then by e-WOMAC. In order to eliminate the possible bias because of patients' potential memory, e-WOMAC and p-WOMAC evaluation will be taken for each patient at 15 minutes apart in the first and third stage. This study has been registered in Chinese Clinical Trial Registry (ChiCTR2100050914) and will be conducted in strict accordance with Chinese ethical laws and regulations.

Blinding

Because of the nature of the study protocol, blinding method will not be used in this study. The data collection and analysis will be carried out by a single researcher

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who is not aware of the study grouping and intervention arrangements.

Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) patients who meet the KOA diagnostic criteria of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint Surgery Group of the Orthopaedic Society of the Chinese Medical Association; (2) patients aged 40 to 70 years, including 40 and 70 years, male or female; (3) KL classification $\leqslant$ grade 3; (4) patients who have a mobile phone and can use the application proficiently; (5) patients who understand Chinese language and can complete the WOMAC independently; (6) patients who have signed the informed consent.

Exclusion criteria are as follows: (1) patients with acute meniscus injury, peripheral ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of knee joint, tuberculosis, idiopathic osteonecrosis of the knee; (2) patients with serious cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other hemorrhagic diseases, mental illness, pregnancy and lactation; (3) patients who are allergic or intolerant to trial medication; (4) Patients who had received other treatments in the last 2 months has an effect on the study; (5) patients who are deemed unsuitable for the clinical trial.

Sample size calculation

The sample size is calculated with based on a small sample pre-test we carried out in the early stage and the sample size calculation method studied by Bellamy et al.[24]. The differences between e-WOMAC and p-WOMAC scores were expressed as the mean scores (with standard errors) as 2.95 (5.53). Consequently, with a type I error at 0.05 and type II error at 0.10 considering a 1:1 allocation rate and a drop-out rate of 10%, the minimum number of participants needed was 35 per group; a total of 70 subjects.

The formula for calculating sample size is as follows:

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$$n = \frac{(t_\alpha + t_\beta)^2 \sigma^2}{\delta^2}$$

Instrument

WOMAC is a widely used self-administered evaluation tool, which can be completed within 5-10 minutes. Research shows that this scale has objective reliability, effectiveness and sensitivity for evaluation of the knee joint, and it is an evaluation scale that has been widely used for patients with OA. The WOMAC rating scale assesses the structure and function of the hip and knee in terms of pain, stiffness, and joint function. There are 24 items in all covering the basic symptoms and signs of OA, 5 items for the pain part, 2 items for the stiffness part, and 17 items for the joint function part, among which each item has a scale bar without scale line, representing the range of 0-10 points, the starting point on the left side of the scale is 0 point, representing none, and the end point on the right side is 10 points, representing extreme severity.[25] The regular paper-based WOMAC requires the patient to fill out based on his or her symptoms and signs within 48 hours, which is then measured by a physician based on the location. E-WOMAC, a Chinese-language electronic scale for self-assessment of patients with KOA, used in the study was developed by Shanghai Jsure Health Co. The text portion of e-WOMAC is identical to WOMAC VAS 3.1. For the first time, the patient needs to scan the QR code and download the Epdata software. After registration and login, patients can fill in the electronic version of WOMAC (figure.2), swipe the ruler on the screen according to their symptoms and signs within 48 hours, and submit after completing the answers. Doctors can directly receive the score data of patients in the Epdata database (figure.3).

Additional Questions

In the end of the study, a simple questionnaire has been designed to investigate subjects' perceptions of the study and the propensity for paper-based or electronic version of WOMAC. The questions will involve the description of the advantages and disadvantages of two WOMACs.

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Interventions

Other medications and treatments for KOA, including oral medications, topical plasters, acupuncture, acupotomy, and arthroscopy will not be available during the study period. If the patient needs additional treatment, they need to contact the doctor in advance. To increase the participation of the patients, we make sure all the treatment of the subjects during the study is free of charge, and the subjects in the trial can have X-ray and MRI images free of charge and receive appropriate transportation subsidy. During the intervention, taking celecoxib has a very small probability of certain digestive tract symptoms, such as vomiting and constipation. The investigator will make every effort to prevent and treat any harm that may result from this study. If adverse events occur in the clinical trial, a committee of medical experts will determine whether it is associated with the treatment. The sponsor will provide the cost of treatment and the corresponding financial compensation for the damage related to the trial in accordance with the Provisions of China's "Standard of Quality Management of Clinical Trials for Drugs". Moreover, we need them to record their medication-taking behavior in time so as to improve their adherence to the study which helps minimize the error.

Primary outcomes

The primary outcome of the current study is the mean score difference in WOMAC. This method has been found to be a semi-quantitative rating scale with better reliability and validity and more balanced empirical evidence. [18] The Chinese e-WOMAC which contains 24 different items split up into 3 subscales: pain subscale (5 items), stiffness subscale (2 items) and physical function subscale (17 items) will be asked to patients. Primary outcomes will be analyzed and reported in two ways. First, we will compare the difference in the respective score of e-WOMAC and p-WOMAC before and after the intervention. Then, we will investigate patients' acceptance of two forms of the WOMAC through a simple self-made questionnaire.

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Secondary outcomes

Additionally, the secondary outcomes include the WOMAC VAS 3.1 Pain Scale (ranging from 0 (no pain during movement) to 500 (extreme pain during movement)), the WOMAC Stiffness Scale (ranging from 0 to 200 with higher scores meaning more severe limitation) and the WOMAC Physical Function Scale (ranging from 0 to 1700, with higher scores indicating more serious impairment during activities). The secondary outcome analyses will be assessed similarly to the main endpoint analyses.

Data collection and management

We will gather information at every stage of recruitment, randomization and treatment so that we can report flow of patients according to the CONSORT guidelines. Once a subject is enrolled or randomized, the study site will make every reasonable effort to follow the subject for the entire study period. Considering the purpose of this study, the data of subjects with complete efficacy data before and after treatment will be included in the statistical analysis.

The paper questionnaire will be completed by subjects alone and data will be collected by trained investigators, then reached the database. The electronic questionnaire will be completed by subjects alone via the smartphone application. The score of e-WOMAC will be entered into an excel file and then analyzed by SPSS. Note that time intervals between two assessments should be 15 minutes in order to eliminate the influence of memory and maintain data quality and objectivity.

Statistical analysis

The aim of the study is to describe a randomized trial designed to test the effectiveness and reliability of mobile phone application for assessment of KOA compared with traditional mode of pen-and-paper based, episodic, onsite evaluation. As the average scores of the two versions of the outcome measures are the same, there may also be significant differences in the scores of individual respondents, and/or differences on certain items. The total score and each dimension of e-WOMAC and p-

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WOMAC will be separately analyzed. All data analysis will be performed by SPSS17.0 statistics software, mean ± standard deviation (SD) is used to described the metrological data following the normal distribution while median (M) and interquartile range (Q) are used to described the data not following the normal distribution.

First, two conditions will be compared at baseline with a between-group analysis via a t-test in order to ensure there is no difference between randomization groups. To test our hypothesis, in the first stage calculate difference scores of each participant (difference d = paper WOMAC score - electronic WOMAC score) and the data will be analyzed for normality by the Shapiro-Wilks test. For the primary outcomes we will use the total WOMAC score directly, while for the secondary outcomes WOMAC subscale scores will be rescaled to a 0-100 scale before calculation. A paired t-test will be used to calculate the mean score difference if data is normally distributed, and the results will be reported as 95% confidence intervals between differences in means, if not, Wilcoxon rank-sum test will be used. Two factor ANOVA model will be used to account for any differences due to the order of completing the paper and electronic WOMAC index. In the third stage, the same statistical analysis will be performed after the intervention the same as the first stage in order to investigate whether the WOMAC score of both high and low levels of KOA has good consistency.

To test the consistency of two versions of the WOMAC, an allowed range is defined (i.e. a value for the mean difference that needed to be exceeded to determine that the two WOMACs are not equivalent). As there is great inter-individual variability between different patients, a limit of equivalence will be determined based on the outcome measure of the pre-experiment to provide a strict test of the equivalence of two WOMACs. If the mean (and its 95% confidence interval) of the difference falls within the allowable ranges, then we can gain the credible evidence of equivalence of scoring system of the WOMAC.

Answers to open-ended questions will be subjected to a simple content analysis, categorized as positive, negative, or neutral comments on the e-WOMAC or p-WOMAC.

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For the condition of shedding samples that may occur in the current study, we will have strict criterion and the statistical analysis will only include patients who participate in the whole process of the study from enrollment to post-intervention assessment.

Data monitoring

An external data monitoring committee was not deemed to be necessary for this trial. Data will be monitored by the research team which includes clinicians, statisticians and information technology experts. This study is considered to be a low-risk trial where both the intervention and control groups will receive their usual medical care. The expected duration of the trial lasts only 1 month and the use of the application does not present with high risk, there won't be any stopping guidelines to terminate the trial nor interim analysis planned.

Patient and public involvement

This research is planned to be done without patient involvement. The patients will not be invited to comment on the study design or be consulted on developing patient-relevant outcomes. The future manuscript will not be edited by patients for readability or accuracy.

Discussion

Since KOA is characterized by chronic progressive degeneration of articular cartilage, its assessment involves a complex process and requires an overall evaluation of the patients' condition for a better clinical outcome. However today in China, many residents don't have the access to family doctors, so they usually need to go to hospital for treatment. The inconvenience in visiting doctors may cause delay in treatment. Smartphone application for electronic data capture appears to be an innovative and promising alternative to the original assessment methods as smartphone application have already been proved to be accurate tools.

However, it would be unwise to consider transforming a traditional paper-based patient-reported outcomes measure to an electronic version for use in the clinical

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practice and research if the equivalence of the two versions hasn't been proved. In this study protocol, we describe an unblinded trial designed to test a newly developed technology-based KOA assessment consisting of a mobile phone application for patients, which is linked to the physicians. Specifically, we want to explore the reliability and comparability of electronic and paper versions of the WOMAC and whether EDC can help improve treatment adherence by meeting patients' preferences.

To the best of our knowledge, this is the first study to test the reliability of the Chinese electronic WOMAC for KOA assessment. If our hypothesis is confirmed, the findings will serve to demonstrate the equivalence of electronic and paper versions of WOMAC and patients' acceptance of Chinese e-WOMAC so that it can be implemented in clinical practice and research. Likewise, our results will further demonstrate the feasibility of e-health for the personalized KOA therapy. (i.e. timely adjustment of the treatment plan can be rapidly given patients based on self-reported ePRO with the help of smartphone application)

We anticipate that with the support of EDC, physicians will be able to receive timely feedback on patients' conditions, which will significantly improve the visiting rate and treatment rate due to the convenience of telemedicine and rapid response to unwanted events. Note that KOA is a common chronic disease in the elderly, the study will explore the feasibility of enabling the Chinese e-WOMAC for patients' long-term use.

However, using EDC systems may still have some limitations. The degree of familiarity with the electronics is not entirely consistent between different population, especially considering the factors of age, social status and other general factors. For example, some patients who don't have communication vehicles or cannot permit proper use of the application may be excluded from online medical service. In addition, psychological factors may have a relevant influence on filling out the questionnaire leading to the condition that patients feel non-adapted, have difficulty in using the smartphone or even failed to complete the questionnaire.[26] [19] Accordingly, we can make some necessary adjustments of the application. In sum, the results of the present investigation may help to find new ways of developing

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smartphone application and information and communication technology in the medical field.

Data management and oversight

In order to ensure protocol compliance, proper study management, and timely completion of study procedures, members of the research team from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine will take responsibility for the conduct of all research staff and study participants.

Protocol and registration

The trial is registered with the ChiCTR, ChiCTR2100050914. Registered on 8 Sep 2021, https://www.chictr.org.cn/showproj.aspx?proj=133521

Data storage security and patient confidentiality

Patients' medical records (descriptive characteristics like name initials, allocated study number, sex, age, BMI, outcome measures like primary outcomes and secondary outcomes and laboratory results) will be kept in the respective hospital, and physicians will document the findings of the study in it, allowing researchers and ethics committees to access the data. Personal information of patients will not be revealed in the results of this study, and we will try everything we can to protect patients' privacy and medical data within the Chinese law. According to medical research ethics, experimental data especially personal privacy information will not be allowed to be accessed and shared by the public and will be limited to web-based databases to ensure that personal privacy information is not disclosed.

Ethics and dissemination

The protocol for this trial has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01). All participants will be required to sign an informed consent form before enrollment in this study. The model consent form and other related documentation given to participants can be provided upon request. (see online supplementary file)

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Abbreviations

KOA: Knee osteoarthritis; WOMAC: Western Ontario and McMaster Universities Arthritis Index; e-WOMAC: electronic version of the WOMAC; p-WOMAC: paper-based WOMAC; e-health: online medical system; PRO: patient-reported outcomes; EDC： electronic data capture; SGH: Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

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Authors' contributions

YJZ and YZ are the co-first authors. WAY, YXZ and HSZ designed the study. YJZ, YZ, KQL and YLC interpreted data. YJZ was responsible for writing of report, literature search, and selection of relevant articles. FL was responsible for the technical service of e-WOMAC.

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Disclaimer

The funding organization has not played any role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation of the manuscript.

Competing interests

The authors declare that they have no competing interests. This study is public welfare, we only entrust Shanghai Jsure Health Co. to provide e-WOMAC software based on the technical advantages of the company.

Patient consent for publication

Not required

Availability of data and material

The datasets analyzed during the current study will be available from the corresponding author on reasonable request.

Consent for publication

Not applicable

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Figure Legend

Figure1: Flow chart of the study

Figure2: Examples of the web for the subjects

(a) the Chinese e-WOMAC app interface after login;

(b) location of knee osteoarthritis: The picture shows the assessed joint（‘您不舒服的地方’means where do you feel uncomfortable？‘左膝’means left knee;‘右膝’means right knee ;‘双膝’means both sides of knee);

(c) e-WOMAC assessment of pain intensity: The picture shows a question about the level of the pain up and down the stairs in the WOMAC pain subscale.(‘上楼梯或下楼梯’ means go upstairs and downstairs. Then choose pain level according to your feelings, the right end of the scale bar means extreme pain and the left means no pain.)

Figure3: Examples of the web for the physician (a)details and operation of subjects’ data; (b)the score of each question; (c)total score as well as pain, stiffness and physical function subscale scores of e-WOMAC.

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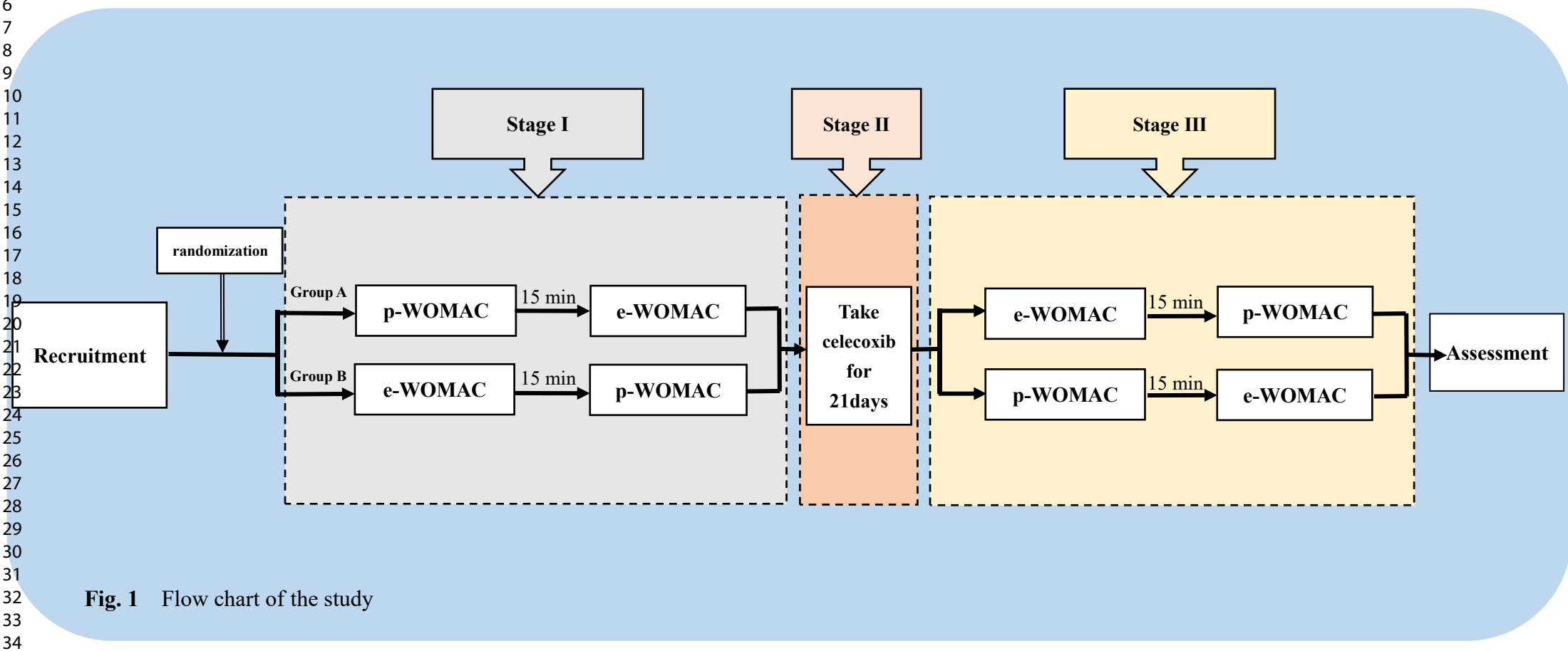

Fig. 1 Flow chart of the study

(a) (b) (c)

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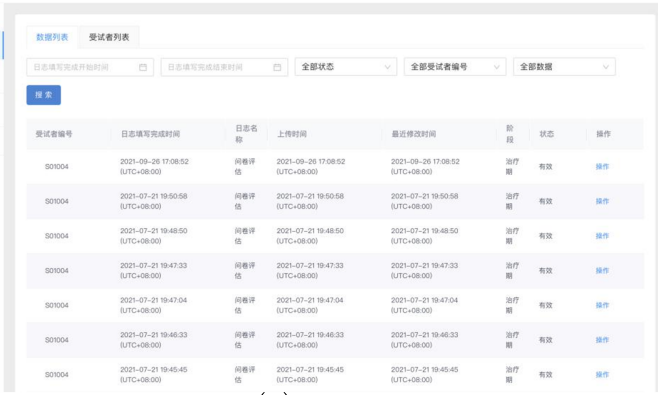

(a)

(b)

(c)

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Informed Consent•informed consent page

Dear Sir/Madam ：

You are invited to participate in the study "**Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: a randomized controlled clinical trial**".

Read the instructions on this page carefully which can help you understand the study including the procedure and duration of the study, and the benefits, risks and discomforts that may be brought to you after participating in it and why it was conducted, before you decide whether or not to take part in this research study. Discuss it with friends and relatives if you wish, or please consult your doctor to help you to reach a decision.

Introduction

Background and Study Aims

Knee osteoarthritis (KOA) is the most common chronic, progressive and degenerative joint disease in middle and old age. It is characterized by articular cartilage degeneration, osteosclerosis and hyperplasia. Major clinical manifestations of KOA include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the lower limb and affect patients' normal life and work. The worldwide prevalence of KOA is increasing, reported to be between 3.8% in 2010, and with an estimated 25,000 people suffer from KOA in 2018. There is radiographic evidence of knee osteoarthritis in up to 14% in asymptomatic uninjured adults aged < 40 years and 43% of middle-aged population. In China, approximately 8.1% of Chinese people are affected by KOA. KOA can greatly affect the patients' health and quality of life. Today, its incidence tends to increase with the advent of an aging society. With increased demand for health, people are becoming more aware of the need for early diagnosis, timely intervention, minimal damage and better prognosis. Patient-reported outcomes (PRO) can truly reflect patients' health status and treatment outcomes, and have played a significant part in diagnosis and treatment for chronic progressive diseases.

By this research, we aim to provide conclusive evidence for developing patient-centered online health application. We hypothesize that the equivalent between two formats of the WOMAC(paper based WOMAC index and electronic WOMAC index) will be proved, then our study objectives is to assess: 1.The comparability of results generated from these two WOMACs. 2.Subjects' acceptance and satisfaction with the Chinese electronic WOMAC index.

This study will be conducted at Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (1 clinical research center) in China. A total of 70 patients volunteered to participate in this study. This research project is supported by the Shanghai Municipal Health Commission (Project No. 201940063). The protocol for this trial has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01) and complies with relevant provisions of Helsinki Declaration on the protection of the rights and interests of subjects.

Inclusion and exclusion criteria

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Inclusion criteria

① patients who meet the KOA diagnostic criteria of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint Surgery Group of the Orthopaedic Society of the Chinese Medical Association;

②patients aged 40 to 70 years, including 40 and 70 years, male or female;

③KL classification≤ grade 3；

④patients who have a mobile phone and can use the application proficiently;

⑤ patients who understand Chinese language and can complete the WOMAC independently;

⑥patients who have signed the informed consent;

Exclusion criteria

① patients with acute meniscus injury, peripheral ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of knee joint, tuberculosis, idiopathic osteonecrosis of the knee;

② patients with serious cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other hemorrhagic diseases, mental illness, pregnancy and lactation;

③patients who are allergic or intolerant to trial medication;

④ Patients who had received other treatments in the last 2 months has an effect on the study;

⑤patients who are deemed unsuitable for the clinical trial.

What do you need to do if you participate in this study?

1、If you meet the inclusion criteria and agree to participate, the study will be conducted as follows:

After you have determined that you can participate in this study, you will have a treatment plan developed by your clinician and perfect routine laboratory tests. In the first stage, you will be evaluated by paper version of WOMAC index and electronic version of WOMAC index on day 1, In the second stage, 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. In the third stage, you will complete both scales again and the tendency questionnaire, and count changes in the condition in the hospital and during follow-up. In addition to this, you do not need laboratory tests such as blood tests throughout your study. Your research doctor will give you health guidance, and you can always contact your research doctor for any questions you may have related to knee osteoarthritis.

2、Other things you need to cooperate with:

During the study period, without affecting your health and daily life, please not to use any kind of medication including analgesics that might affect the study outcomes. If you need additional treatment for various reasons, please also provide us with the relevant information.

Benefits from participating in the study

Participating in this clinical study, your condition may improve. You can get more medical advice and guidance related to this disease as you proceed with this trial.

Your participation will also contribute to the research of rehabilitation exercises for knee osteoarthritis, which is of social significance for the treatment of this disease and for other patients with such diseases.

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Risks from participation in this study

This study was designed as a interventional study. During the intervention, taking celecoxib has a very small probability of certain digestive tract symptoms, such as vomiting and constipation.

If you experience any discomfort during the study, there is a new change in your condition or any unexpected circumstances, whether or not related to the study, you should promptly notify your doctor, who will judge and give appropriate medical treatment.

During the study period, you need to follow up at the hospital on time and do some tests, which take up some of your time and may cause trouble or inconvenience.

Costs and compensation for study participation

Patients do not need to pay out-of-pocket expenses for the diagnosis and treatment of KOA in clinical trials. Additionally, there will be no financial compensation for the study participation because the examination items in this study are clinical follow-up programs.

If adverse events occur in the clinical trial, a committee of medical experts will determine whether it is associated with the treatment. The sponsor will provide the cost of treatment and the corresponding financial compensation for the damage related to the trial in accordance with the Provisions of China's "Standard of Quality Management of Clinical Trials for Drugs".

The evaluation, diagnosis and treatment required for combined diseases will not be covered free of charge.

Is personal information confidential?

Information about your participation in this study will be recorded in the study medical records/case report form. All the medical record of the original studies including descriptive characteristics like name initials, allocated study number, sex, age, BMI, outcome measures like primary outcomes and secondary outcomes and laboratory results are treated with standard medical confidentiality and confidential to the extent allowed by law.

In the clinical record form, only your name initials and allocated study number will appear. In relevant research summaries, articles, and public journals, only the initials and numbers of your name will appear if necessary.

When necessary, pharmaceutical supervisory and administrative departments, the ethical committee and the project funding department may consult the information of the subjects participating in the study according to regulations. However, they would not use the data of the participants in the study for other purposes or leak it to other groups without permission.

How to get more information?

You can ask any questions about this study at any time.

Your doctor will leave you his/her phone number so that he/she can answer your questions。

If there is any important new information during the course of the study that may affect your willingness to continue with the study, your doctor will notify you in a timely manner.

You may voluntarily choose to participate in the study and quit the study halfway

Whether you participate in this research is entirely voluntary. You are free to refuse to participate in this study or to withdraw at any time without affecting any benefits to which you

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would otherwise be entitled and be discriminated against or be subject to any reprisal.

Your doctor or researcher may suspend your participation in this study at any time for the best interest of the subject. You may be consulted about your use of the study drug if you quit the study for any reason.

If clinician feel examination is required, you may also be asked for physical examination and laboratory tests. You may also refuse without discrimination or retaliation for it.

If you choose to participate in this study, we expect you to complete the research.

If you do not participate in this study, your research physician will provide you with alternative treatment options, such as other drug or exercise therapies for knee osteoarthritis.

What should you do at the present time?

It is up to you to decide whether or not to participate in this study. You can discuss with your family or friends and ask your doctor as many questions as possible until you fully understand the study before making a decision.

Ethics committee

If you have questions or need to ask anyone other than the investigator, please consult the Ethics Committee of Shanghai Shuguang Hospital.

Ethics Committee Office: The second floor of the eastern administration of Shuguang Hospital

Tel.: 20256070

Thank you for reading the above material. If you decide to participate in this study, tell your doctor and he/she will arrange everything for you to do with the study.

Please keep this information sheet.

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Informed Consent•consent signature page

Project name: Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: a randomized controlled clinical trial

Project source: Shanghai Municipal Health Commission

Project version: V1.0

Project date: January 10, 2019

Consent statement

I have read the above statements of this study and were given the chance to discuss the study with and ask questions to the investigator. Any questions I had were answered to my full satisfaction.

I am aware of the risks and benefits that may arise from participating in this study. I am aware that participation in the study is on a voluntary basis. I have had enough time to think about my participation in the study, and I understand that:

- I can always ask the doctor for more information.
- I can withdraw from the study at any time without detriment, and medical care and treatment will not be affected.

I was also very much aware that if I tell the doctor about the change in my condition and complete the physical examination and laboratory test particularly for reasons of drug in case of dropout, it will be very beneficial to me and the whole research.

In case any other treatment needed, I will call for a doctor's opinion in advance or tell the doctor truthfully afterwards

I give permission for pharmaceutical supervisory and administrative departments, the ethical committee and the project funding department to have access to my research materials.

I will receive a copy of the signed and dated written informed consent form.

Finally, I agree to participate in the study and try to conform to the advice of the doctors as far as possible.

Subjects Signature：_____ Date：_____

Subjects Tel.：_____

I confirmed that the entire protocol of this study was explained to all subjects, including their rights, risks and benefits, and were given a signed copy of the informed consent form.

Investigator Signature：_____ Date：_____

Investigator Tel.：_____

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

Section/item	ItemNo	Description	Page and Line Number	Reason if not applicable
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page1 Line1	
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page1 Line35	
	2b	All items from the World Health Organization Trial Registration Data Set	Page1 Line35	
Protocol version	3	Date and version identifier	Page1 Line36	
Funding	4	Sources and types of financial, material, and other support	Page15 Line27	
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page15 Line18	
	5b	Name and contact information for the trial sponsor	Page1 Line10	

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	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		n/a This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
	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)		n/a Coordinating centre, steering committee, endpoint adjudication committee, data management team will not have any role in this protocol.
Introduction			Page2 Line16	
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	Page4 Line19	
	6b	Explanation for choice of comparators		n/a There is not a control group in this study.
Objectives	7	Specific objectives or hypotheses	Page4 Line22	
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, noninferiority, exploratory)	Page5 Line2	

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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	Page6 Line5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page7 Line6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page6 Line15
	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)	Page9 Line10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page9 Line17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page9 Line4

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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	Page9 Line21
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)	see Figure1
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	Page7 Line26
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page6 Line4

Methods: Assignment of interventions (for controlled trials)

Allocation:

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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	Page6 Line11	
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	Page6 Line12	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page6 Line13	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page7 Line3	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		n/a Blinding method will not be used in this study.

Methods: Data collection, management, and analysis

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Data collection methods	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	Page10 Line14
	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	Page10 Line17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page10 Line16
Statistical methods	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	Page10 Line20

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	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page8 Line29	
	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)		n/a Considering the purpose of this study, the data of subjects with complete efficacy data before and after treatment will be included in the statistical analysis.
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page12 Line13	
	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	Page12 Line17	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page9 Line16	

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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		n/a This clinical trial will not include auditing.
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page14 Line24	
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)		n/a The preliminary experiments of this research group and the similar types of research by others have proved the feasibility of the research.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page6 Line10	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		n/a This experiment does not involve biological specimens.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page14 Line21	

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page16 Line16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page14 Line28
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	Page9 Line17
Dissemination policy	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	Page16 Line23
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page16 Line25
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page16 Line23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement matertial

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Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a This experiment does not involve biological specimens.

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

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Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: protocol for a randomized controlled clinical trial

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Manuscripts

Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: protocol for a randomized controlled clinical trial

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Abstract

Introduction: The Western Ontario and McMaster University osteoarthritis index (WOMAC) is the most commonly used indicator of disease-specific outcome in knee osteoarthritis for its convenience and reliability. It has two formats the paper-based WOMAC (p-WOMAC) and the electronic WOMAC (e-WOMAC). In China, the p-WOMAC has been widely used though e-WOMAC is yet untested. This study aims to test whether e-WOMAC is consistent with the p-WOMAC before and after the intervention.

Methods and analysis: A total of 70 patients from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine will be randomly assigned in two groups named group A and group B. This study is divided into three stages. In the first stage, patients in group A will be evaluated first by p-WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC and then by p-WOMAC. In the second stage of the study, drug interventions will be implemented. 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. In the third stage, post-intervention evaluation will be conducted after administration. Patients in group A will be evaluated first by e-WOMAC and then by p-WOMAC. Patients in group B will be evaluated first by p-WOMAC and then by e-WOMAC. In order to avoid the possible bias because of patients' potential memory, e-WOMAC and p-WOMAC will be taken for each patient at 15 minutes apart. The primary outcome of the study is the mean score difference in WOMAC, and the secondary outcomes are the score differences in WOMAC subscales: pain, stiffness, and physical function.

Ethics and dissemination: The protocol has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01). The results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: ChiCTR2100050914

Protocol version: 1.0, 20 November 2021

Strengths and limitations of this study

The study approach and design enable a comprehensive analysis of the reliability and comparability of paper-based and Chinese electronic version of WOMAC in normal clinical practice in a Chinese population.

This study is a randomized, crossover design with intervention that can verify whether e-WOMAC is the same as p-WOMAC in sensitively reflecting the actual changes in patients' conditions.

In this study, patient satisfaction was added as an outcome to investigate subjects' propensity for paper-based or Chinese electronic version of WOMAC.

As the instruments will be collected using electronic tablets, a certain level of computer literacy is required, and the study may not be able to include participants who are not capable of handling the devices.

Since the patients with KL classification ⩽ grade 3 KOA were included in the study, the results will not be valid for severe KOA patients.

Introduction

Knee osteoarthritis (KOA) is the most common chronic, progressive and degenerative joint disease in middle and old age. It is characterized by articular cartilage degeneration, osteosclerosis and hyperplasia.[1] Major clinical manifestations of KOA include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the lower limb and affect patients' normal life and work.[2]

The worldwide prevalence of KOA is increasing, reported to be between 3.8% in 2010, and with an estimated 25,000 people suffer from KOA in 2018.[3] [4] There is radiographic evidence of knee osteoarthritis in up to 14% of asymptomatic uninjured adults aged <40 years and 43% of the middle-aged population.[5] In China, approximately 8.1% of Chinese people are affected by KOA.[6] KOA can greatly affect the patient's health and quality of life. Today, its incidence tends to increase with the advent of an aging society.[7] With increased focus on health, people are becoming

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more aware of the need for early diagnosis, timely intervention, minimal damage and better prognosis. Patient-reported outcomes (PRO) can truly reflect patients' health status and treatment outcomes, and have played a significant part in the diagnosis and treatment of chronic progressive diseases. The Western Ontario and McMaster University osteoarthritis (WOMAC) index invented by Bellamy is a specific PRO scale, which has high reliability and sensitivity for KOA severity assessment and can accurately reflect the patient's symptoms and functional limitations, and it is also less affected by subjective factors of the patients.[8] For those who have mild symptoms of OA, it shows high reliability and is currently the most widely used tool to assess the severity level of KOA.[9]

Although the paper-based WOMAC has already been accepted and widely used, there are still several shortcomings, such as difficulties in collecting and analyzing pen and paper-based data. Especially when it comes to the quality of clinical research, traditional paper-based data is hard to be accessed retrospectively. In times of Information Technology and communication technologies, smartphone application provides the technical basis for online assessment and telemedicine.[10] [11] [12] Meanwhile, another method of collecting PRO data or mode of administration (MOA), PRO collected and recorded using the electronic data capture(EDC) tool came into being and received increasing attention in recent years. Nowadays, many different forms of WOMAC on the mobile phone, tablet or pc appear in large numbers, namely electronic WOMAC (e-WOMAC), which has been favored by researchers and become a very useful tool for objective assessment of KOA in clinical practice and research gradually.[13] [14]

The visual analogue scale (VAS) is used in e-WOMAC for the assessment of KOA. Pain, stiffness and dysfunction assessment can be completed directly at any time at home through e-WOMAC application, and then physicians can rapidly understand the patient's condition and adapt treatment to achieve personalized healthcare by telemedicine.[15] The main advantages of the e-WOMAC include high efficiency, lower data collection error rate, faster response and

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increased response rates.[16] [17] [18] [19] Practically, online medical service is potentially beneficial for patients with KOA: electronic questionnaire can be completed almost anytime and anyplace, alleviating the influence of environmental factors. The online medical models of care also avoid multiple visits to the clinic. Additionally, paper-less records reduce the waste of resources, which is beneficial for the environment.

Before being put into use, many countries, including the UK, Australia, Switzerland and Austria, have demonstrated the reliability of the e-WOMAC because the difference in MOA may induce bias, even when the index is consistent across modes. R.Theiler argues that English e-WOMAC has similar responsiveness in detecting clinically meaningful change to the traditional p-WOMAC.[20] HA Bischoff-Ferrari makes a similar point in his study of consistency between German e-WOMAC with the original format as well.[21] Similarly, R.Theiler found that the Swiss computerized WOMAC 3.1 and conventional p-WOMAC are similar in all three subscales.[22] Overall, these studies illustrate the point that electronic MOA is a promising alternative to the traditional mode.

In China, the existing body of research on the Chinese paper-based WOMAC numerical rating scale (NRS) 3.1 suggests its psychological robustness in reliability and validity.[23] The research also shows that compared with the Lysholm score, IKDC score, HSS score, KSS score and other scales used in the assessment of KOA, Chinese WOMAC 3.1 is the most suitable assessment scale. However, the Chinese electronic WOMAC hasn't been put into use, so research to date has not yet determined the equivalence of Chinese e-WOMAC and the traditional p-WOMAC.

Objective

By this research, we aim to evaluate the electronic mode of administration and provide conclusive evidence for developing patient-centered online health applications. We hypothesize that the equivalent between two formats of the WOMAC will be proved, then our study objective is to assess: 1. The comparability of results generated

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from these two WOMACs. 2. Subjects' acceptance and satisfaction with the Chinese e-WOMAC index.

Method

Study design

This study is a randomized controlled trial (RCT) that aims to evaluate the consistency between the Chinese electronic WOMAC (e-WOMAC) and paper WOMAC (p-WOMAC) evaluations of patients with knee osteoarthritis (KOA). The study schedule of enrollment, interventions and assessments are shown in Table1. The start and end of the study was planned for September 2021 and December 2023, respectively.

Table 1 Study schedule of enrolment, interventions and assessments.

STUDY PERIOD			
	Pre-intervention	**Intervention period**	**Close-out**
TIMEPOINT	**T_0** Pre-intervention	**T_1** Between assessments	**T_2** One month follow-up
ENROLMENT:			
Eligibility screen	√		
Informed consent	√		
Allocation	√		
INTERVENTION:			
Medical treatment		√	
P-WOMAC analysis	√		√
E-WOMAC analysis	√		√
ASSESSMENTS:			
Demographics	√		
Primary outcomes			

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WOMAC total score	√	√
Secondary outcomes		
WOMAC pain score	√	√
WOMAC stiffness score	√	√
WOMAC function score	√	√

Recruitment and Randomization

A total of 70 patients with KOA will be recruited from the Orthopedic Clinic of Shuguang Hospital affiliated to SHUTCM. The KOA patient will receive a clinical examination by an orthopedic surgeon. Patients with KOA meeting the inclusion criteria will be given detailed information of this study. The importance of patients' active participation in the study and self-monitoring of the disease will be emphasized to improve their enthusiasm. All participants will be provided with an information sheet and sign the informed consent by a research nurse. After participation acceptance, the patients will be divided into group A and group B by randomly generated computer numbers, with 35 patients in each group. A researcher not involved in patient care will prepare and administer the randomization schedule. Neither the researchers nor the patients will be blinded to the evaluation and treatment assignment.

Figure.1 provides an overview of the flow of study. The study is divided into three stages. In the first stage (T0), patients in group A will be evaluated first by p-WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC and then by p-WOMAC. In the second stage of the study, drug interventions will be implemented. 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. The third stage is the consistency evaluation stage after intervention. The post-intervention evaluation will be conducted after administration on day 21 (T2). Patients in group A will be evaluated first by e-WOMAC and then by paper WOMAC. Patients in group B will be evaluated first by p-WOMAC and then by e-WOMAC. In order to eliminate the possible bias because of patients' potential memory, e-WOMAC and p-WOMAC evaluation will be taken for

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each patient at 15 minutes apart in the first and third stage. This study has been registered in Chinese Clinical Trial Registry (ChiCTR2100050914) and will be conducted in strict accordance with Chinese ethical laws and regulations.

Blinding

Because of the nature of the study protocol, the blinding method will not be used in this study. The data collection and analysis will be carried out by a single researcher who is not aware of the study grouping and intervention arrangements.

Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) patients who meet the KOA diagnostic criteria of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint Surgery Group of the Orthopaedic Society of the Chinese Medical Association; (2) patients aged 40 to 70 years, including 40 and 70 years, male or female; (3) KL classification $\leqslant$ grade 3; (4) patients who have a mobile phone and can use the application proficiently; (5) patients who understand Chinese language and can complete the WOMAC independently; (6) patients who have signed the informed consent.

Exclusion criteria are as follows: (1) patients with acute meniscus injury, peripheral ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of knee joint, tuberculosis, idiopathic osteonecrosis of the knee; (2) patients with serious cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other hemorrhagic diseases, mental illness, pregnancy and lactation; (3) patients who are allergic or intolerant to trial medication; (4) Patients who had received other treatments in the last two months has an effect on the study; (5) patients who are deemed unsuitable for the clinical trial.

Sample size calculation

The sample size is calculated based on a small sample pre-test we carried out in

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the early stage and the sample size calculation method studied by Bellamy et al.[24]. The differences between e-WOMAC and p-WOMAC scores were expressed as the mean scores (with standard errors) as 2.95 (5.53). Consequently, with a type I error at 0.05 and type II error at 0.10, considering a 1:1 allocation rate and a drop-out rate of 10%, the minimum number of participants needed was 35 per group, a total of 70 subjects.

The formula for calculating sample size is as follows:

$$n = \frac{(t_\alpha + t_\beta)^2 \sigma^2}{\delta^2}$$

Instrument

WOMAC is a widely used self-administered evaluation tool, which can be completed within 5-10 minutes. Research shows that this scale has objective reliability, effectiveness and sensitivity for evaluation of the knee joint, and it is an evaluation scale that has been widely used for patients with OA. The WOMAC rating scale assesses the structure and function of the hip and knee in terms of pain, stiffness, and joint function. There are 24 items in all covering the basic symptoms and signs of OA, 5 items for the pain part, 2 items for the stiffness part, and 17 items for the joint function part, among which each item has a scale bar without a scale line, representing the range of 0-10 points, the starting point on the left side of the scale is 0 point, representing none, and the end point on the right side is 10 points, representing extreme severity.[25] The regular paper-based WOMAC requires the patient to fill out based on his or her symptoms and signs within 48 hours, which is then measured by a physician based on the location. E-WOMAC, a Chinese-language electronic scale for self-assessment of patients with KOA, used in the study was developed by Shanghai Jsure Health Co. The text portion of e-WOMAC is identical to WOMAC VAS 3.1. For the first time, the patient needs to scan the QR code and download the Epdata software. After registration and login, patients can fill in the electronic version of WOMAC (figure.2), swipe the ruler on the screen according to their symptoms and signs within 48 hours, and submit after completing the answers. Doctors can directly receive the score data of patients in the Epdata database (figure.3).

Additional Questions

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At the end of the study, a simple questionnaire has been designed to investigate subjects' perceptions of the study and the propensity for the paper-based or electronic version of WOMAC. The questions will involve the description of the advantages and disadvantages of two WOMACs.

Interventions

Other medications and treatments for KOA, including oral medications, topical plasters, acupuncture, acupotomy, and arthroscopy will not be available during the study period. If the patient needs additional treatment, they need to contact the doctor in advance. To increase the participation of the patients, we make sure all the treatment of the subjects during the study is free of charge, and the subjects in the trial can have X-ray and MRI images free of charge and receive appropriate transportation subsidy. During the intervention, taking celecoxib has a very small probability of certain digestive tract symptoms, such as vomiting and constipation. The investigator will make every effort to prevent and treat any harm that may result from this study. If adverse events occur in the clinical trial, a committee of medical experts will determine whether it is associated with the treatment. The sponsor will provide the cost of treatment and the corresponding financial compensation for the damage related to the trial in accordance with the Provisions of China's "Standard of Quality Management of Clinical Trials for Drugs". Moreover, we need them to record their medication-taking behavior in time so as to improve their adherence to the study, which helps minimize the error.

Primary outcomes

The primary outcome of the current study is the mean score difference in WOMAC. This method has been found to be a semi-quantitative rating scale with better reliability and validity and more balanced empirical evidence. [18] The Chinese e-WOMAC, which contains 24 different items split up into 3 subscales: pain subscale (5 items), stiffness subscale (2 items), and physical function subscale (17 items) will be

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asked to patients. Primary outcomes will be analyzed and reported in two ways. First, we will compare the difference in the respective score of e-WOMAC and p-WOMAC before and after the intervention. Then, we will investigate patients' acceptance of two forms of the WOMAC through a simple self-made questionnaire.

Secondary outcomes

Additionally, the secondary outcomes include the WOMAC VAS 3.1 Pain Scale (ranging from 0 (no pain during movement) to 500 (extreme pain during movement)), the WOMAC Stiffness Scale (ranging from 0 to 200 with higher scores meaning more severe limitation) and the WOMAC Physical Function Scale (ranging from 0 to 1700, with higher scores indicating more serious impairment during activities). The secondary outcome analyses will be assessed similarly to the main endpoint analyses.

Data collection and management

We will gather information at every stage of recruitment, randomization and treatment so that we can report flow of patients according to the CONSORT guidelines. Once a subject is enrolled or randomized, the study site will make every reasonable effort to follow the subject for the entire study period. Considering the purpose of this study, the data of subjects with complete efficacy data before and after treatment will be included in the statistical analysis.

The paper questionnaire will be completed by subjects alone, and data will be collected by trained investigators, then reach the database. The electronic questionnaire will be completed by subjects alone via the smartphone application. The score of e-WOMAC will be entered into an excel file and then analyzed by SPSS. Note that time intervals between two assessments should be 15 minutes in order to eliminate the influence of memory and maintain data quality and objectivity.

Statistical analysis

The aim of the study is to describe a randomized trial designed to test the

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effectiveness and reliability of mobile phone application for the assessment of KOA compared with the traditional mode of pen and paper-based, episodic, onsite evaluation. As the average scores of the two versions of the outcome measures are the same, there may also be significant differences in the scores of individual respondents, and/or differences on certain items. The total score and each dimension of e-WOMAC and p-WOMAC will be separately analyzed. All data analysis will be performed by SPSS17.0 statistics software, mean ± standard deviation (SD) is used to describe the metrological data following the normal distribution, while median (M) and interquartile range (Q) are used to describe the data not following the normal distribution.

First, two conditions will be compared at baseline with a between-group analysis via a t-test in order to ensure there is no difference between randomization groups. To test our hypothesis, in the first stage calculate the difference scores of each participant (difference d = paper WOMAC score - electronic WOMAC score) and the data will be analyzed for normality by the Shapiro-Wilks test. For the primary outcomes, we will use the total WOMAC score directly, while for the secondary outcomes, WOMAC subscale scores will be rescaled to a 0-100 scale before calculation. A paired t-test will be used to calculate the mean score difference if data is normally distributed, and the results will be reported as 95% confidence intervals between differences in means; if not, Wilcoxon rank-sum test will be used. Two-factor ANOVA model will be used to account for any differences due to the order of completing the paper and electronic WOMAC index. In the third stage, statistical analysis will be performed after the intervention the same as in the first stage in order to investigate whether the WOMAC score of both high and low levels of KOA has good consistency.

To test the consistency of two versions of the WOMAC, an allowed range is defined (i.e., a value for the mean difference that needed to be exceeded to determine that the two WOMACs are not equivalent). As there is great inter-individual variability between different patients, a limit of equivalence will be determined based on the outcome measure of the pre-experiment to provide a strict test of the equivalence of

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two WOMACs. If the mean (and its 95% confidence interval) of the difference falls within the allowable ranges, then we can gain credible evidence of the equivalence of the scoring system of the WOMAC.

Answers to open-ended questions will be subjected to a simple content analysis, categorized as positive, negative, or neutral comments on the e-WOMAC or p-WOMAC.

For the condition of shedding samples that may occur in the current study, we will have strict criterion and the statistical analysis will only include patients who participate in the whole process of the study from enrollment to post-intervention assessment.

Data monitoring

An external data monitoring committee was not deemed to be necessary for this trial. Data will be monitored by the research team, which includes clinicians, statisticians and information technology experts. This study is considered to be a low-risk trial where both the intervention and control groups will receive their usual medical care. The expected duration of the trial lasts only 1 month and the use of the application does not present with high risk, there won't be any stopping guidelines to terminate the trial or interim analysis planned.

Patient and public involvement

This research is planned to be done without patient involvement. The patients will not be invited to comment on the study design or be consulted on developing patient-relevant outcomes. The future manuscript will not be edited by patients for readability or accuracy.

Discussion

Since KOA is characterized by chronic progressive degeneration of articular cartilage, its assessment involves a complex process and requires an overall evaluation of the patient's condition for a better clinical outcome. However, today in China, many residents don't have access to family doctors, so they usually need to go to hospital for treatment. The inconvenience of visiting doctors may cause delay in treatment.

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Smartphone application for electronic data capture appears to be an innovative and promising alternative to the original assessment methods, as smartphone application have already been proved to be accurate tools.

However, it would be unwise to consider transforming a traditional paper-based patient-reported outcomes measure to an electronic version for use in clinical practice and research if the equivalence of the two versions hasn't been proved. In this study protocol, we describe an unblinded trial designed to test a newly developed technology-based KOA assessment consisting of a mobile phone application for patients, which is linked to the physicians. Specifically, we want to explore the reliability and comparability of electronic and paper versions of the WOMAC and whether electronic MOA can help improve treatment adherence by meeting patients' preferences.

To the best of our knowledge, this is the first study to test the reliability of the Chinese electronic WOMAC for KOA assessment. If our hypothesis is confirmed, the findings will serve to demonstrate the equivalence of electronic and paper versions of WOMAC and patients' acceptance of Chinese e-WOMAC so that it can be implemented in clinical practice and research. Likewise, our results will further demonstrate the feasibility of e-health for personalized KOA therapy. (i.e., timely adjustment of the treatment plan can be rapidly given to patients based on self-reported ePRO with the help of a smartphone application)

We anticipate that with the support of electronic MOA, physicians will be able to receive timely feedback on patients' conditions, which will significantly improve the visiting rate and treatment rate due to the convenience of telemedicine and rapid response to unwanted events. Note that KOA is a common chronic disease in the elderly, the study will explore the feasibility of enabling the Chinese e-WOMAC for patients' long-term use.

However, using EDC systems may still have some limitations. The degree of familiarity with the electronics is not entirely consistent between different populations, especially considering the factors of age, social status and other general factors. For example, some patients who don't have communication vehicles or cannot permit proper use of the application may be excluded from the online medical service.

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In addition, psychological factors may have a relevant influence on filling out the questionnaire leading to the condition that patients feel non-adapted, have difficulty in using the smartphone or even fail to complete the questionnaire.[26] Accordingly, we can make some necessary adjustments to the application. In sum, the results of the present investigation may help to find new ways of developing smartphone applications and information and communication technology in the medical field. In addition, it will also be more favorable to select the most appropriate MOA for PROs, including electronic MOA, paper-based MOA or mixed-mode designs.

Data management and oversight

In order to ensure protocol compliance, proper study management, and timely completion of study procedures, members of the research team from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine will take responsibility for the conduct of all research staff and study participants.

Protocol and registration

The trial is registered with the ChiCTR, ChiCTR2100050914. Registered on 8 Sep 2021, https://www.chictr.org.cn/showproj.aspx?proj=133521

Data storage security and patient confidentiality

Patient's medical records (descriptive characteristics like name initials, allocated study number, sex, age, BMI, outcome measures like primary outcomes and secondary outcomes and laboratory results) will be kept in the respective hospital, and physicians will document the findings of the study in it, allowing researchers and ethics committees to access the data. Personal information of patients will not be revealed in the results of this study, and we will try everything we can to protect patients' privacy and medical data within Chinese law. According to medical research ethics, experimental data, especially personal privacy information, will not be allowed to be accessed and shared by the public and will be limited to web-based databases to ensure that personal privacy information is not disclosed.

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Ethics and dissemination

The protocol for this trial has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01). All participants will be required to sign an informed consent form before enrollment in this study. The model consent form and other related documentation given to participants can be provided upon request. (see online supplementary file)

Abbreviations

KOA: Knee osteoarthritis; WOMAC: Western Ontario and McMaster Universities Arthritis Index; e-WOMAC: electronic version of the WOMAC; p-WOMAC: paper-based WOMAC; e-health: online medical system; PRO: patient-reported outcomes; EDC: electronic data capture; SGH: Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

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Authors' contributions

YJZ and YZ are the co-first authors. WAY, YXZ and HSZ designed the study. YJZ, YZ, KQL and YLC interpreted data. YJZ was responsible for the writing of report, literature search, and selection of relevant articles. FL was responsible for the technical service of e-WOMAC.

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Disclaimer

The funding organization has not played any role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation of the manuscript.

Competing interests

The authors declare that they have no competing interests. This study is the public welfare, we only entrust Shanghai Jsure Health Co. to provide e-WOMAC software based on the technical advantages of the company.

Patient consent for publication

Not required

Availability of data and material

The datasets analyzed during the current study will be available from the corresponding author on reasonable request.

Consent for publication

Not applicable

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Figure Legend

Figure1: Flow chart of the study

Figure2: Examples of the web for the subjects

(a) the Chinese e-WOMAC app interface after login;

(b) location of knee osteoarthritis: The picture shows the assessed joint（‘您不舒服的地方’means where do you feel uncomfortable？‘左膝’means left knee;‘右膝’means right knee;‘双膝’means both sides of knee);

(c) e-WOMAC assessment of pain intensity: The picture shows a question about the level of the pain up and down the stairs in the WOMAC pain subscale. (‘上楼梯或下楼梯’ means go upstairs and downstairs. Then choose pain level according to your feelings, the right end of the scale bar means extreme pain and the left means no pain.)

Figure3: Examples of the web for the physician (a)details and operation of subjects’ data; (b)the score of each question; (c)total score as well as pain, stiffness and physical function subscale scores of e-WOMAC.

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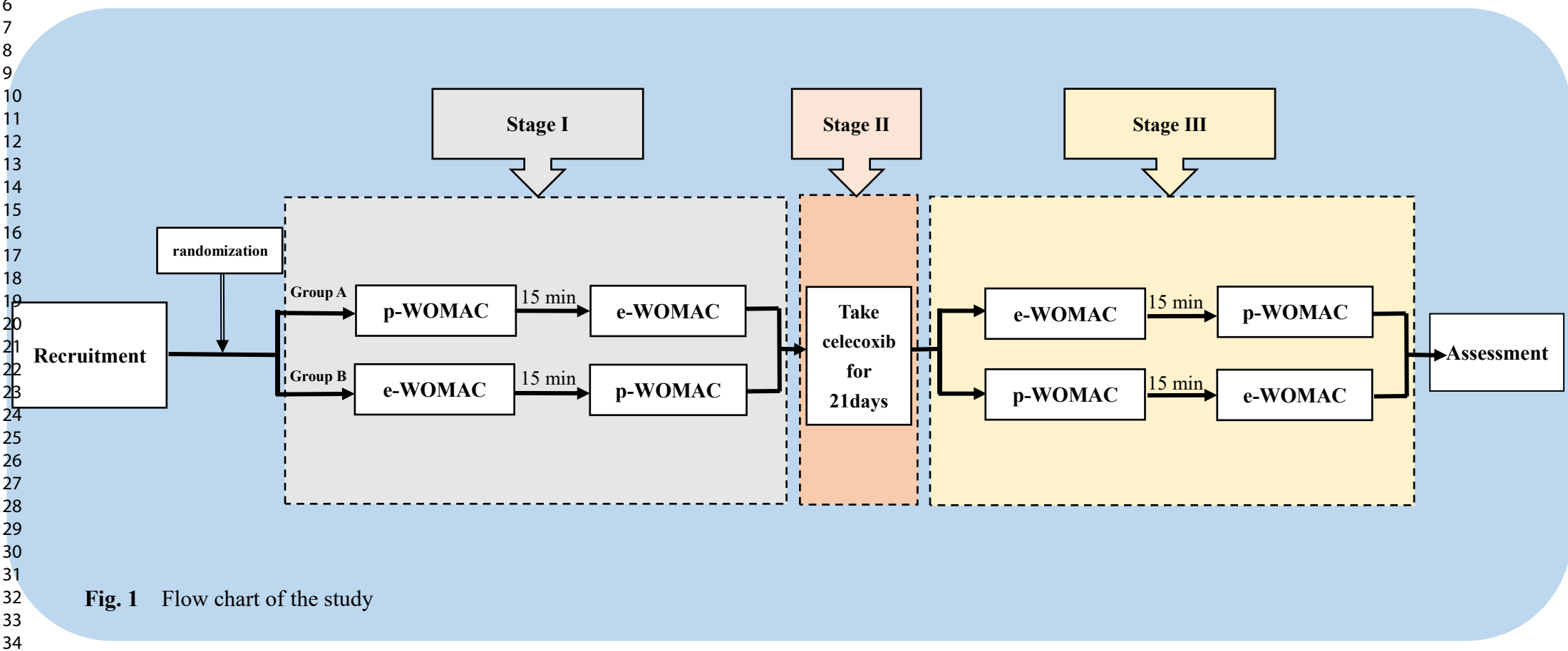

Fig. 1 Flow chart of the study

(a) (b) (c)

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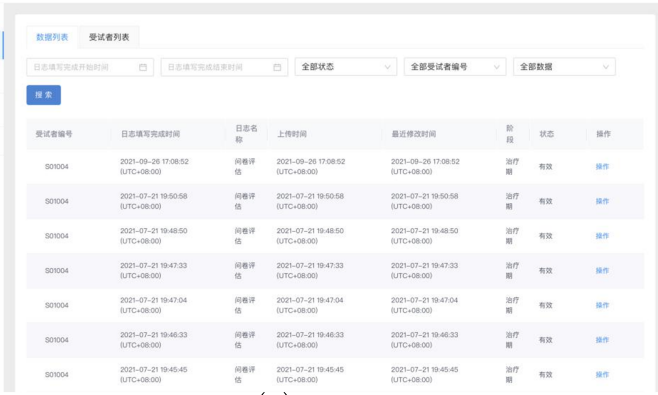

(a)

(b)

(c)

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Informed Consent•informed consent page

Dear Sir/Madam ：

You are invited to participate in the study "**Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: a randomized controlled clinical trial**".

Read the instructions on this page carefully which can help you understand the study including the procedure and duration of the study, and the benefits, risks and discomforts that may be brought to you after participating in it and why it was conducted, before you decide whether or not to take part in this research study. Discuss it with friends and relatives if you wish, or please consult your doctor to help you to reach a decision.

Introduction

Background and Study Aims

Knee osteoarthritis (KOA) is the most common chronic, progressive and degenerative joint disease in middle and old age. It is characterized by articular cartilage degeneration, osteosclerosis and hyperplasia. Major clinical manifestations of KOA include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the lower limb and affect patients' normal life and work. The worldwide prevalence of KOA is increasing, reported to be between 3.8% in 2010, and with an estimated 25,000 people suffer from KOA in 2018. There is radiographic evidence of knee osteoarthritis in up to 14% in asymptomatic uninjured adults aged < 40 years and 43% of middle-aged population. In China, approximately 8.1% of Chinese people are affected by KOA. KOA can greatly affect the patients' health and quality of life. Today, its incidence tends to increase with the advent of an aging society. With increased demand for health, people are becoming more aware of the need for early diagnosis, timely intervention, minimal damage and better prognosis. Patient-reported outcomes (PRO) can truly reflect patients' health status and treatment outcomes, and have played a significant part in diagnosis and treatment for chronic progressive diseases.

By this research, we aim to provide conclusive evidence for developing patient-centered online health application. We hypothesize that the equivalent between two formats of the WOMAC(paper based WOMAC index and electronic WOMAC index) will be proved, then our study objectives is to assess: 1.The comparability of results generated from these two WOMACs. 2.Subjects' acceptance and satisfaction with the Chinese electronic WOMAC index.

This study will be conducted at Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (1 clinical research center) in China. A total of 70 patients volunteered to participate in this study. This research project is supported by the Shanghai Municipal Health Commission (Project No. 201940063). The protocol for this trial has been approved by the Independent Review Board of SGH (approval number: 2020-814-21-01) and complies with relevant provisions of Helsinki Declaration on the protection of the rights and interests of subjects.

Inclusion and exclusion criteria

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Inclusion criteria

① patients who meet the KOA diagnostic criteria of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint Surgery Group of the Orthopaedic Society of the Chinese Medical Association;

②patients aged 40 to 70 years, including 40 and 70 years, male or female;

③KL classification≤ grade 3；

④patients who have a mobile phone and can use the application proficiently;

⑤ patients who understand Chinese language and can complete the WOMAC independently;

⑥patients who have signed the informed consent;

Exclusion criteria

① patients with acute meniscus injury, peripheral ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of knee joint, tuberculosis, idiopathic osteonecrosis of the knee;

② patients with serious cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other hemorrhagic diseases, mental illness, pregnancy and lactation;

③patients who are allergic or intolerant to trial medication;

④ Patients who had received other treatments in the last 2 months has an effect on the study;

⑤patients who are deemed unsuitable for the clinical trial.

What do you need to do if you participate in this study?

1、If you meet the inclusion criteria and agree to participate, the study will be conducted as follows:

After you have determined that you can participate in this study, you will have a treatment plan developed by your clinician and perfect routine laboratory tests. In the first stage, you will be evaluated by paper version of WOMAC index and electronic version of WOMAC index on day 1, In the second stage, 200mg celecoxib will be administered orally once a day starting from the second day of enrollment for a period of 21 days. In the third stage, you will complete both scales again and the tendency questionnaire, and count changes in the condition in the hospital and during follow-up. In addition to this, you do not need laboratory tests such as blood tests throughout your study. Your research doctor will give you health guidance, and you can always contact your research doctor for any questions you may have related to knee osteoarthritis.

2、Other things you need to cooperate with:

During the study period, without affecting your health and daily life, please not to use any kind of medication including analgesics that might affect the study outcomes. If you need additional treatment for various reasons, please also provide us with the relevant information.

Benefits from participating in the study

Participating in this clinical study, your condition may improve. You can get more medical advice and guidance related to this disease as you proceed with this trial.

Your participation will also contribute to the research of rehabilitation exercises for knee osteoarthritis, which is of social significance for the treatment of this disease and for other patients with such diseases.

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Risks from participation in this study

This study was designed as a interventional study. During the intervention, taking celecoxib has a very small probability of certain digestive tract symptoms, such as vomiting and constipation.

If you experience any discomfort during the study, there is a new change in your condition or any unexpected circumstances, whether or not related to the study, you should promptly notify your doctor, who will judge and give appropriate medical treatment.

During the study period, you need to follow up at the hospital on time and do some tests, which take up some of your time and may cause trouble or inconvenience.

Costs and compensation for study participation

Patients do not need to pay out-of-pocket expenses for the diagnosis and treatment of KOA in clinical trials. Additionally, there will be no financial compensation for the study participation because the examination items in this study are clinical follow-up programs.

If adverse events occur in the clinical trial, a committee of medical experts will determine whether it is associated with the treatment. The sponsor will provide the cost of treatment and the corresponding financial compensation for the damage related to the trial in accordance with the Provisions of China's "Standard of Quality Management of Clinical Trials for Drugs".

The evaluation, diagnosis and treatment required for combined diseases will not be covered free of charge.

Is personal information confidential?

Information about your participation in this study will be recorded in the study medical records/case report form. All the medical record of the original studies including descriptive characteristics like name initials, allocated study number, sex, age, BMI, outcome measures like primary outcomes and secondary outcomes and laboratory results are treated with standard medical confidentiality and confidential to the extent allowed by law.

In the clinical record form, only your name initials and allocated study number will appear. In relevant research summaries, articles, and public journals, only the initials and numbers of your name will appear if necessary.

When necessary, pharmaceutical supervisory and administrative departments, the ethical committee and the project funding department may consult the information of the subjects participating in the study according to regulations. However, they would not use the data of the participants in the study for other purposes or leak it to other groups without permission.

How to get more information?

You can ask any questions about this study at any time.

Your doctor will leave you his/her phone number so that he/she can answer your questions。

If there is any important new information during the course of the study that may affect your willingness to continue with the study, your doctor will notify you in a timely manner.

You may voluntarily choose to participate in the study and quit the study halfway

Whether you participate in this research is entirely voluntary. You are free to refuse to participate in this study or to withdraw at any time without affecting any benefits to which you

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would otherwise be entitled and be discriminated against or be subject to any reprisal.

Your doctor or researcher may suspend your participation in this study at any time for the best interest of the subject. You may be consulted about your use of the study drug if you quit the study for any reason.

If clinician feel examination is required, you may also be asked for physical examination and laboratory tests. You may also refuse without discrimination or retaliation for it.

If you choose to participate in this study, we expect you to complete the research.

If you do not participate in this study, your research physician will provide you with alternative treatment options, such as other drug or exercise therapies for knee osteoarthritis.

What should you do at the present time?

It is up to you to decide whether or not to participate in this study. You can discuss with your family or friends and ask your doctor as many questions as possible until you fully understand the study before making a decision.

Ethics committee

If you have questions or need to ask anyone other than the investigator, please consult the Ethics Committee of Shanghai Shuguang Hospital.

Ethics Committee Office: The second floor of the eastern administration of Shuguang Hospital

Tel.: 20256070

Thank you for reading the above material. If you decide to participate in this study, tell your doctor and he/she will arrange everything for you to do with the study.

Please keep this information sheet.

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Informed Consent•consent signature page

Project name: Test reliability and comparability of paper and Chinese electronic version of the Western Ontario and McMaster University osteoarthritis index: a randomized controlled clinical trial

Project source: Shanghai Municipal Health Commission

Project version: V1.0

Project date: January 10, 2019

Consent statement

I have read the above statements of this study and were given the chance to discuss the study with and ask questions to the investigator. Any questions I had were answered to my full satisfaction.

I am aware of the risks and benefits that may arise from participating in this study. I am aware that participation in the study is on a voluntary basis. I have had enough time to think about my participation in the study, and I understand that:

- I can always ask the doctor for more information.
- I can withdraw from the study at any time without detriment, and medical care and treatment will not be affected.

I was also very much aware that if I tell the doctor about the change in my condition and complete the physical examination and laboratory test particularly for reasons of drug in case of dropout, it will be very beneficial to me and the whole research.

In case any other treatment needed, I will call for a doctor's opinion in advance or tell the doctor truthfully afterwards

I give permission for pharmaceutical supervisory and administrative departments, the ethical committee and the project funding department to have access to my research materials.

I will receive a copy of the signed and dated written informed consent form.

Finally, I agree to participate in the study and try to conform to the advice of the doctors as far as possible.

Subjects Signature：_____ Date：_____

Subjects Tel.：_____

I confirmed that the entire protocol of this study was explained to all subjects, including their rights, risks and benefits, and were given a signed copy of the informed consent form.

Investigator Signature：_____ Date：_____

Investigator Tel.：_____

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

Section/item	ItemNo	Description	Page and Line Number	Reason if not applicable
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page1 Line1	
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page1 Line35	
	2b	All items from the World Health Organization Trial Registration Data Set	Page1 Line35	
Protocol version	3	Date and version identifier	Page1 Line36	
Funding	4	Sources and types of financial, material, and other support	Page15 Line7	
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page16 Line1	
	5b	Name and contact information for the trial sponsor	Page1 Line11	

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	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		n/a This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
	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)		n/a Coordinating centre, steering committee, endpoint adjudication committee, data management team will not have any role in this protocol.
Introduction			Page2 Line16	
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	Page4 Line22	
	6b	Explanation for choice of comparators		n/a There is not a control group in this study.
Objectives	7	Specific objectives or hypotheses	Page4 Line23	
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, noninferiority, exploratory)	Page5 Line5	

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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	Page6 Line7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page7 Line10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page6 Line19
	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)	Page9 Line18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page9 Line23
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page9 Line10

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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	Page9 Line27
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)	see Figure1
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	Page7 Line28
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page6 Line10

Methods: Assignment of interventions (for controlled trials)

Allocation:

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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	Page6 Line13	
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	Page6 Line14	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page6 Line15	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page7 Line5	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		n/a Blinding method will not be used in this study.

Methods: Data collection, management, and analysis

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Data collection methods	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	Page10 Line25
	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	Page10 Line27
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page10 Line24
Statistical methods	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	Page11 Line2

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	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page9 Line3	
	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)		n/a Considering the purpose of this study, the data of subjects with complete efficacy data before and after treatment will be included in the statistical analysis.
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page12 Line17	
	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	Page12 Line21	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page9 Line20	

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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		n/a This clinical trial will not include auditing.
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page15 Line9	
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)		n/a The preliminary experiments of this research group and the similar types of research by others have proved the feasibility of the research.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page6 Line12	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		n/a This experiment does not involve biological specimens.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page14 Line26	

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page16 Line26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page15 Line1
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	Page9 Line20
Dissemination policy	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	Page16 Line33
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page16 Line35
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page16 Line33
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement matertial

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Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a This experiment does not involve biological specimens.

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

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