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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 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

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4 This is the first study to evaluate the impact of Chinese WOMAC index in normal
5 clinical practice in a Chinese population.
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8 It is an effectiveness-implementation hybrid trial that aims to promote more
9 effective and patient-centred care of people with KOA.
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12 Utilizing modern technology, this study seeks to overcome implementation
13 barriers by gathering and analyzing WOMAC index as related to the general population
14 to produce a patient-filled report.
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18 Based on the results of this study, routine WOMAC data collection can be
19 integrated into electronic medical records if it is effective.
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23 As the instruments will be collected using electronic tablets, a certain level of
24 computer literacy is required, and the study may not be able to include participants who
25 are not capable of handling the devices
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31 **Introduction**

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33 Knee osteoarthritis (KOA) is the most common chronic, progressive and
34 degenerative joint disease in middle and old age. It is characterized by articular cartilage
35 degeneration, osteosclerosis and hyperplasia. Major clinical manifestations of KOA
36 include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation
37 of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the
38 lower limb and affect patients' normal life and work. ¹ In China, approximately
39 3% of Chinese people are affected by OA, mostly KOA. There is radiographic evidence
40 of knee osteoarthritis in up to 60% of middle-aged population. People over 65 years old
41 even have a 25% higher incidence rate. KOA can greatly affect the patients' health and
42 quality of life. Today, its incidence tends to increase with the advent of an aging society.
43 ²⁻³ With increased demand for health, people are becoming more aware of the need for
44 early diagnosis, timely intervention, minimal damage and better prognosis. Patient-
45 reported outcomes (PRO) can truly reflect patients' health status and treatment
46 outcomes, and have played a significant part in diagnosis and treatment for chronic
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4 progressive diseases. The WOMAC is a specific PRO scale, which has high reliability
5 and sensitivity for KOA severity assessment and can accurately reflect the patients'
6 symptoms and functional limitations, while having little influence on the subjective
7 tendency of the patients.⁴ For those who have mild symptoms of OA, it shows high
8 reliability and is currently the most widely used tool to assess severity level of KOA.⁵
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14 Although the paper-based WOMAC has already been accepted and widely used,
15 there are still several shortcomings such as difficulties of collecting and analyzing pen-
16 and-paper based data. Especially when it comes to the quality of clinical research,
17 traditional paper-based data is hard to be accessed retrospectively. In times of IT and
18 communication technologies, smartphone application provides technical basis for
19 online assessment and telemedicine.⁶⁻⁸ Nowadays, many different forms of WOMAC
20 on the mobile phone, tablet or pc are emerged in large numbers, namely electronic
21 WOMAC (e-WOMAC) which have been favored by researchers and become the first
22 choice of assessment of KOA in the clinical practice and research.
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31 The visual analogue scale (VAS) is used in e-WOMAC for assessment of KOA.
32 Pain, stiffness and dysfunction assessment can be completed directly at any time at
33 home through e-WOMAC application and then physicians can rapidly
34 understand patient's condition and adapt treatment to achieve personalized healthcare
35 by telemedicine.⁹ The main advantages of the e-WOMAC include high efficiency,
36 lower data collection error rate, shorter response time and increased response rates.¹⁰⁻
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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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4 meaningful change than the traditional p-WOMAC. ¹⁴ HA Bischoff-Ferrari makes a
5 similar point in his study of consistency between German e-WOMAC with the original
6 format as well. ¹⁵ Similarly, R.Theiler found that the Swiss computerized WOMAC 3.1
7 and conventional p-WOMAC are similar in all three subscale. ¹⁶ Overall, these studies
8 illustrate the heterogeneity that electronic data capture (EDC) is a promising alternative
9 to traditional paper-based mode.
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15 In China, the existing body of research on the Chinese paper-based WOMAC
16 numerical rating scale (NRS) 3.1 suggests its psychological robustness in reliability and
17 validity. ¹⁷ The research also shows that compared with Lysholm score, IKDC
18 score, HSS score, KSS score and other scale used in assessment of KOA, Chinese
19 WOMAC 3.1 is the most suitable assessment scale. However, the Chinese electronic
20 WOMAC hasn't been put into use, so research to date has not yet determined the
21 equivalence of Chinese e-WOMAC and the traditional p-WOMAC.
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30 **Objective**

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

46 **Study design**

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48 This study is a randomised controlled trial (RCT) aims to evaluate the consistency
49 between the Chinese electronic WOMAC (e-WOMAC) and paper WOMAC (p-
50 WOMAC) evaluations of patients with knee osteoarthritis (KOA). The study schedule
51 of enrollment, interventions and assessments are shown in **Table1**.
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60 **Table 1** Study schedule of enrolment, interventions and assessments.

STUDY PERIOD			
	Pre-intervention	Intervention period	Close-out
TIMEPOINT	T₀	T₁	T₂
	Pre-intervention	Between assessments	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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4 to improve their enthusiasm. All participants will be provided with an information sheet
5 and sign the informed consent. After participation acceptance, the patients will be
6 divided into two groups by randomly generated computer numbers, 120 patients in each
7 group. Neither the researchers nor the patients will be blinded to the evaluation and
8 treatment assignment.
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13 **Figure.1** provides an overview of the flow of study. The study is divided into
14 three stages. In the first stage (T0) patients in group A will be evaluated first by p-
15 WOMAC and then by e-WOMAC. Patients in group B will be evaluated by e-WOMAC
16 and then by p-WOMAC. In the second stage of the study, drug interventions will be
17 implemented. 200mg celecoxib will be administered orally once a day starting from the
18 second day of enrollment for a period of 21 days. The third stage is the consistency
19 evaluation stage after intervention. The post-intervention evaluation will be conducted
20 after administration on day 21 (T2). Patients in group A will be evaluated first by e-
21 WOMAC and then by paper WOMAC. Patients in group B will be evaluated first by
22 p-WOMAC and then by e-WOMAC. In order to eliminate the possible bias because of
23 patients' potential memory, e-WOMAC and p-WOMAC evaluation will be taken for
24 each patient at 15 minutes apart in the first and third stage. This study has been
25 registered in Chinese Clinical Trial Registry (ChiCTR2100050914) and will be
26 conducted in strict accordance with Chinese ethical laws and regulations.
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41 **Blinding**

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

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53 Inclusion criteria are as follows: (1) patients who meet the KOA diagnostic criteria
54 of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint
55 Surgery Group of the Orthopaedic Society of the Chinese Medical Association; (2)
56 patients aged 40 to 70 years, including 40 and 70 years, male or female; (3) KL
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4 classification \leq grade 3; (4) patients who have a mobile phone and can use the
5 application proficiently; (5) patients who understand Chinese language and can
6 complete the WOMAC independently; (6) patients who have signed the informed
7 consent.
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11 Exclusion criteria are as follows: (1) patients with acute meniscus injury, peripheral
12 ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of
13 knee joint, tuberculosis, idiopathic osteonecrosis of the knee; (2) patients with serious
14 cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other
15 hemorrhagic diseases, mental illness, pregnancy and lactation; (3) patients who are
16 allergic or intolerant to trial medication; (4) Patients who had received other treatments
17 in the last 2 months has an effect on the study; (5) patients who are deemed unsuitable
18 for the clinical trial.
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29 **Sample size calculation**

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31 There is no previous literature report and the sample size calculation will not be
32 applicable to this study.
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35 **Instrument**

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37 WOMAC is a widely used self-administered evaluation tool, which can be
38 completed within 5-10 minutes. Research shows that this scale has objective reliability,
39 effectiveness and sensitivity for evaluation of the knee joint, and it is an evaluation
40 scale that has been widely used for patients with OA. The WOMAC rating scale
41 assesses the structure and function of the hip and knee in terms of pain, stiffness, and
42 joint function. There are 24 items in all covering the basic symptoms and signs of OA,
43 5 items for the pain part, 2 items for the stiffness part, and 17 items for the joint function
44 part, among which each item has a scale bar without scale line, representing the range
45 of 0-10 points, the starting point on the left side of the scale is 0 point, representing
46 none, and the end point on the right side is 10 points, representing extreme severity.¹⁸
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48 The regular paper-based WOMAC requires the patient to fill out based on his or her
49 symptoms and signs within 48 hours, which is then measured by a physician based on
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4 the location. E-WOMAC, a Chinese-language electronic scale for self-assessment of
5 patients with KOA, used in the study was developed by Shanghai Jsure Health Co. The
6 text portion of e-WOMAC is identical to WOMAC VAS 3.1. For the first time, the
7 patient needs to scan the QR code and download the Epdata software. After registration
8 and login, patients can fill in the electronic version of WOMAC (figure.2), swipe the
9 ruler on the screen according to their symptoms and signs within 48 hours, and submit
10 after completing the answers. Doctors can directly receive the score data of patients in
11 the Epdata database (figure.3).
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20 **Additional Questions**

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

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

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

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

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42 We will try to collect resulting data from all patients in the study, including those
43 who never attend or discontinue therapy, those who discontinue participation in the
44 study and those who get away. We will gather information at every stage of recruitment,
45 randomization and treatment so that we can report flow of patients according to the
46 CONSORT guidelines.
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51 The paper questionnaire will be completed by subjects alone and data will be
52 collected by trained investigators, then reached the database. The electronic
53 questionnaire will be completed by subjects alone via the smartphone application. The
54 score of e-WOMAC will be entered into an excel file and then analyzed by SPSS. Note
55 that time intervals between two assessments should be 15 minutes in order to eliminate
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4 the influence of memory and maintain data quality and objectivity.
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8 **Statistical analysis**

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10 The aim of the study is to describe a randomized trial designed to test the
11 effectiveness and reliability of mobile phone application for assessment of KOA
12 compared with traditional mode of pen-and-paper based, episodic, onsite evaluation.
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14 As the average scores of the two versions of the outcome measures are the same, there
15 may also be significant differences in the scores of individual respondents, and/or
16 differences on certain items. The total score and each dimension of e-WOMAC and p-
17 WOMAC will be separately analyzed. All data analysis will be performed
18 by SPSS17.0 statistics software, mean \pm standard deviation (SD) is used to described
19 the metrological data following the normal distribution while median (M) and
20 interquartile range (Q) are used to described the data not following the normal
21 distribution.
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31 First, two conditions will be compared at baseline with a between-group analysis
32 via a t-test in order to ensure there is no difference between randomization groups.
33 To test our hypothesis, in the first stage calculate difference scores of each participant
34 (difference $d =$ paper WOMAC total score - electronic WOMAC total score) and the
35 data will be analyzed for normality by the Shapiro-Wilks test. A paired t-test will be
36 used to calculate the mean score difference if data is normally distributed, and the
37 results will be reported as 95% confidence intervals between differences in means,
38 if not, Wilcoxon rank-sum test will be used. Two factor ANOVA model will be used to
39 account for any differences due to the order of completing the paper and electronic
40 WOMAC index. In the third stage, the same statistical analysis will be performed after
41 the intervention the same as the first stage in order to investigate whether the WOMAC
42 score of both high and low levels of KOA has good consistency.
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54 To test the consistency of two versions of the WOMAC, an allowed range is
55 defined (i.e. a value for the mean difference that needed to be exceeded to determine
56 that the two WOMACs are not equivalent). As there is great inter-individual variability
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4 between different patients, a limit of equivalence will be determined based on the
5 outcome measure of the pre-experiment to provide a strict test of the equivalence of
6 two WOMACs. If the mean (and its 95% confidence interval) of the difference falls
7 within the allowable ranges, then we can gain the credible evidence of equivalence of
8 scoring system of the WOMAC.
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13 Answers to open-ended questions will be subjected to a simple content analysis,
14 categorized as positive, negative, or neutral comments on the e-WOMAC or p-
15 WOMAC.
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19 For the condition of shedding samples that may occur in the current study, we will
20 have strict criterion and the statistical analysis will only include patients who participate
21 in the whole process of the study from enrollment to post-intervention assessment.
22 Moreover, we need them to record their medication-taking behavior in time so as to
23 improve their adherence to the study which helps minimize the error.
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31 **Data monitoring**

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

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

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4 Since KOA is characterized by chronic progressive degeneration of articular
5 cartilage, its assessment involves a complex process and requires an overall evaluation
6 of the patients' condition for a better clinical outcome. However today in China, many
7 residents don't have the access to family doctors, so they usually need to go to hospital
8 for treatment. The inconvenience in visiting doctors may cause delay in treatment.
9 Smartphone application for electronic data capture appears to be an innovative and
10 promising alternative to the original assessment methods as smartphone application
11 have already been proved to be accurate tools.
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14 However, it would be unwise to consider transforming a traditional paper-based
15 patient-reported outcomes measure to an electronic version for use in the clinical
16 practice and research if the equivalence of the two versions hasn't been proved. In this
17 study protocol, we describe an unblinded trial designed to test a newly developed
18 technology-based KOA assessment consisting of a mobile phone application for
19 patients, which is linked to the physicians. Specifically, we want to explore the
20 reliability and comparability of electronic and paper versions of the WOMAC and
21 whether EDC can help improve treatment adherence by meeting patients' preferences.
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24 To the best of our knowledge, this is the first study to test the reliability of the
25 Chinese electronic WOMAC for KOA assessment. If our hypothesis is confirmed, the
26 findings will serve to demonstrate the equivalence of electronic and paper versions of
27 WOMAC and patients' acceptance of Chinese e-WOMAC so that it can be
28 implemented in clinical practice and research. Likewise, our results will further
29 demonstrate the feasibility of e-health for the personalized KOA therapy. (i.e.
30 timely adjustment of the treatment plan can be rapidly given patients based on self-
31 reported ePRO with the help of smartphone application)
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34 We anticipate that with the support of EDC, physicians will be able to receive
35 timely feedback on patients' conditions, which will significantly improve the
36 visiting rate and treatment rate due to the convenience of telemedicine and rapid
37 response to unwanted events. Note that KOA is a common chronic disease in the elderly,
38 the study will explore the feasibility of enabling the Chinese e-WOMAC for patients'
39 long-term use.
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4 However, using EDC systems may still have some limitations. The degree
5 of familiarity with the electronics is not entirely consistent between different
6 population, especially considering the factors of age, social status and other general
7 factors. For example, some patients who don't have communication vehicles or cannot
8 permit proper use of the application may be excluded from online medical service. In
9 addition, psychological factors may have a relevant influence on filling
10 out the questionnaire leading to the condition that patients feel non-adapted, have
11 difficulty in using the smartphone or even failed to complete the questionnaire.¹⁹
12 Accordingly, we can make some necessary adjustments of the application. In sum, the
13 results of the present investigation may help to find new ways of developing
14 smartphone application and information and communication technology in the medical
15 field.
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29 **Data management and oversight**

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

42 The trial is registered with the ChiCTR, ChiCTR2100050914. Registered on 8 Sep 2021,
43 <https://www.chictr.org.cn/showproj.aspx?proj=133521>
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49 **Data storage security and patient confidentiality**

50 Patients' medical records will be kept in the respective hospital, and physicians will
51 document the findings of the study in it, allowing researchers and ethics committees to
52 access the data. Personal information of patients will not be revealed in
53 the results of this study, and we will try everything we can to protect patients'
54 privacy and medical data within the Chinese law. According to medical research ethics,
55 experimental data especially personal privacy information will not be allowed to be
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4 accessed and shared by the public, and will be limited to web-based databases to ensure
5 that personal privacy information is not disclosed.
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9 **Ethics and dissemination**

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

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

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52 **Authors' contributions**

53 YJZ and YZ are the co-first authors. YJZ, YZ, KQL and YLC interpreted data. YJZ
54 was responsible for writing of report, literature search, and selection of relevant articles.
55 FL was responsible for the technical service of e-WOMAC.
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58

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1
2
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20 **Disclaimer**

21 The funding organisation has not played any role in the design and conduct of the study;
22 collection, management, analysis, or interpretation of the data; or preparation of the
23 manuscript.
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26 **Competing interests**

27 The authors declare that they have no competing interests.
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30 **Patient consent for publication**

31 Not required
32

33 **Availability of data and material**

34 Data sharing is not available to the public as no datasets were generated during the
35 current study.
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39 **Consent for publication**

40 Not applicable.
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7 and McMaster Universities Osteoarthritis Index in Patients From Mainland China With
8 Osteoarthritis of the Knee. *Arthritis Care Res (Hoboken)*. 2015 Nov;67(11):1553-60.

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15 osteoarthritis: the Knee Osteoarthritis Fears and Beliefs Questionnaire (KOFBeQ). *PLoS One*.
16 2013;8(1):e53886.
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21 **Figure Legend**

22 **Figure1: Flow chart of the study**

23 **Figure2: Examples of the web for the subjects**

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

25
26 (b) location of knee osteoarthritis: The picture shows the assessed joint (‘您不舒服
27 的地方’ means where do you feel uncomfortable? ‘左膝’ means left knee; ‘右膝’
28 means right knee ; ‘双膝’ means both sides of knee);

29
30 (c) e-WOMAC assessment of pain intensity: The picture shows a question about the
31 level of the pain up and down the stairs in the WOMAC pain subscale.(‘上楼梯或下
32 楼梯’ means go upstairs and downstairs. Then choose pain level according to your
33 feelings, the right end of the scale bar means extreme pain and the left means no pain.)

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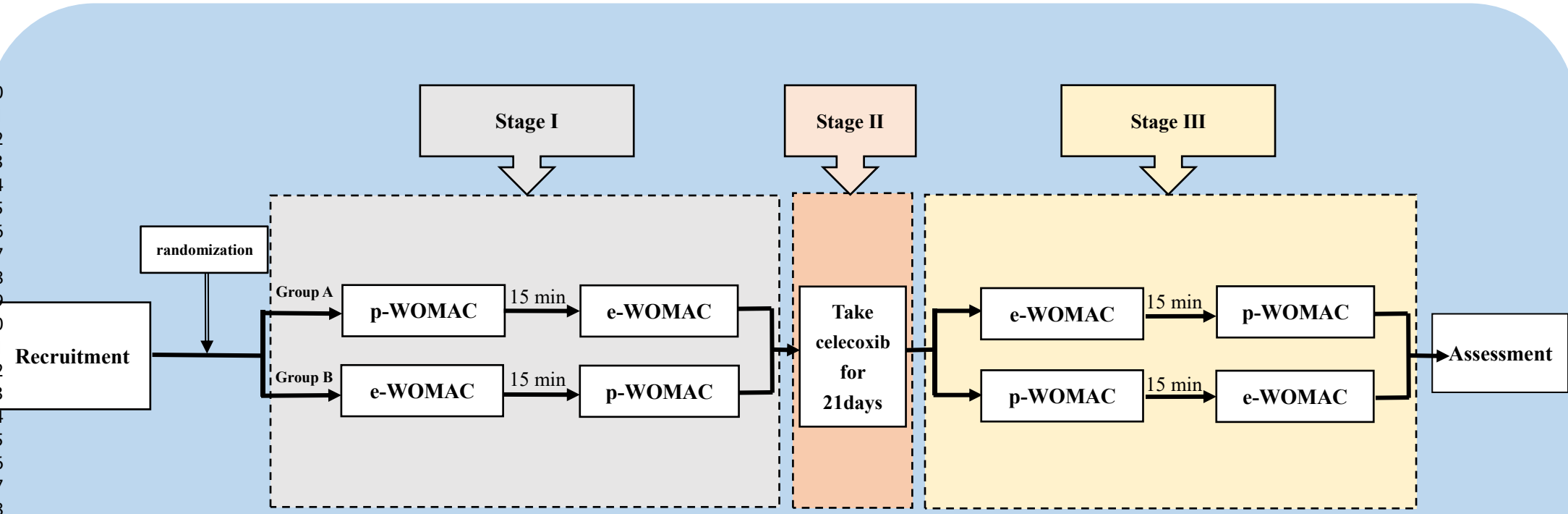


Fig. 1 Flow chart of the study

ePData

点击按钮进入应用

开始

您的医生已经选择了您的研究关节，如果您确定不了哪一处才是您的研究关节，请在填写本调查表以前询问清楚。

您不舒服的地方？

左膝 右膝 双膝

返回

下一步

请根据您在过去48小时内感觉到的膝关节【疼痛程度】将下方的三角滑块滑到合适的位置。

(2) 上楼梯或下楼梯



上一步

下一步

(a)

(b)

(c)

- 1 首页
- 2 报表
- 3 受试者数据
- 4 管理
- 5 注册
- 6 注册
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数据列表 (中心编号:01)

数据列表 受试者列表

日志填写完成开始时间 日志填写完成结束时间 全部状态 全部受试者编号 全部数据

搜索

受试者编号	日志填写完成时间	日志名称	上传时间	最近修改时间	阶段	状态	操作
S01004	2021-09-26 17:08:52 (UTC+08:00)	问卷评估	2021-09-26 17:08:52 (UTC+08:00)	2021-09-26 17:08:52 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:50:58 (UTC+08:00)	问卷评估	2021-07-21 19:50:58 (UTC+08:00)	2021-07-21 19:50:58 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:48:50 (UTC+08:00)	问卷评估	2021-07-21 19:48:50 (UTC+08:00)	2021-07-21 19:48:50 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:47:33 (UTC+08:00)	问卷评估	2021-07-21 19:47:33 (UTC+08:00)	2021-07-21 19:47:33 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:47:04 (UTC+08:00)	问卷评估	2021-07-21 19:47:04 (UTC+08:00)	2021-07-21 19:47:04 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:46:33 (UTC+08:00)	问卷评估	2021-07-21 19:46:33 (UTC+08:00)	2021-07-21 19:46:33 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:45:45 (UTC+08:00)	问卷评估	2021-07-21 19:45:45 (UTC+08:00)	2021-07-21 19:45:45 (UTC+08:00)	治疗期	有效	操作

(a)

日志详情

受试者编号:	S01004
日志名称:	问卷评估
日志填写完成时间:	2021-06-10 20:23:15 (UTC+08:00)
日志上传时间:	2021-06-10 20:23:15 (UTC+08:00)
最近修改时间:	2021-06-10 20:23:15 (UTC+08:00)
阶段:	治疗期
状态:	有效
您不舒服的地方?	
左膝:	
疼痛程度: (1) 在平坦的路上行走	
63;	
疼痛程度: (2) 上楼梯或下楼梯	
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疼痛程度: (3) 晚上,在床上时,就是说打扰您睡觉的疼痛	
60;	
疼痛程度: (4) 弯腰时	
71;	

(b)

23	行动障碍的程度: (23) 做繁重的家务活问题 54;
24	行动障碍的程度: (24) 做轻松的家务活 48;
25	疼痛评分 294;
26	僵硬评分 140;
27	功能评分 1027;
28	womac总评分 1461;

(c)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-063576.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2022
Complete List of Authors:	Zhang, yujie; Shuguang Hospital Zhao, ye; Shuguang Hospital Liu, kaoqiang; Shuguang Hospital Chai, yongli; Shuguang Hospital Lin, fen; Shanghai Jsure Health Co., Ltd Zhan, Hongsheng; Shuguang Hospital Zheng, Yuxin; Shuguang Hospital Yuan, Weian; Shuguang Hospital,
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Health services research, Research methods
Keywords:	Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PRIMARY CARE

SCHOLARONE™
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

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4 This is the first study to evaluate the reliability and comparability of paper-based
5 and Chinese electronic version of WOMAC index in normal clinical practice in a
6 Chinese population.
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10 Moreover, this trial focuses on subjects' propensity for paper-based or Chinese
11 electronic version of WOMAC.
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14 This study is a randomized, crossover design with intervention which can verify
15 whether e-WOMAC is the same as p-WOMAC in sensitively reflecting the actual
16 changes of patients' conditions.
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20 As the instruments will be collected using electronic tablets, a certain level of
21 computer literacy is required, and the study may not be able to include participants who
22 are not capable of handling the devices.
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26 Since the patients with KL classification \leq grade 3 KOA were included in the
27 study, the results will not be valid for severe KOA patients.
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30 31 32 33 **Introduction**

34
35 Knee osteoarthritis (KOA) is the most common chronic, progressive and
36 degenerative joint disease in middle and old age. It is characterized by articular cartilage
37 degeneration, osteosclerosis and hyperplasia.¹ Major clinical manifestations of KOA
38 include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation
39 of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the
40 lower limb and affect patients' normal life and work.²
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48 The worldwide prevalence of KOA is increasing, reported to be between 3.8% in
49 2010, and with an estimated 25,000 people suffer from KOA in 2018.^{3 4} There is
50 radiographic evidence of knee osteoarthritis in up to 14% in asymptomatic uninjured
51 adults aged <40 years and 43% of middle-aged population.⁵ In China, approximately
52 8.1% of Chinese people are affected by KOA.⁶ KOA can greatly affect the patients'
53 health and quality of life. Today, its incidence tends to increase with the advent of an
54 aging society.⁷ With increased focus on health, people are becoming more aware of
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4 the need for early diagnosis, timely intervention, minimal damage and better prognosis.
5 Patient-reported outcomes (PRO) can truly reflect patients' health status and treatment
6 outcomes, and have played a significant part in diagnosis and treatment for chronic
7 progressive diseases. The WOMAC is a specific PRO scale, which has high reliability
8 and sensitivity for KOA severity assessment and can accurately reflect the patients'
9 symptoms and functional limitations, and it is also less affected by subjective factors
10 of the patients.⁸ For those who have mild symptoms of OA, it shows high reliability
11 and is currently the most widely used tool to assess severity level of KOA.⁹

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

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43 The visual analogue scale (VAS) is used in e-WOMAC for assessment of KOA.
44 Pain, stiffness and dysfunction assessment can be completed directly at any time at
45 home through e-WOMAC application and then physicians can rapidly
46 understand patient's condition and adapt treatment to achieve personalized healthcare
47 by telemedicine.¹⁵ The main advantages of the e-WOMAC include high efficiency,
48 lower data collection error rate, faster response and increased response rates.^{16 17 18 19}
49 Practically, online medical service is potentially beneficial for patients with KOA:
50 electronic questionnaire can be completed almost anytime and anyplace alleviating the
51 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

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 **Table 1**. 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	T₀	T₁	T₂
	Pre-intervention	Between assessments	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 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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4 who is not aware of the study grouping and intervention arrangements.
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8 **Inclusion and exclusion criteria**

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10 Inclusion criteria are as follows: (1) patients who meet the KOA diagnostic criteria
11 of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint
12 Surgery Group of the Orthopaedic Society of the Chinese Medical Association; (2)
13 patients aged 40 to 70 years, including 40 and 70 years, male or female; (3) KL
14 classification \leq grade 3; (4) patients who have a mobile phone and can use the
15 application proficiently; (5) patients who understand Chinese language and can
16 complete the WOMAC independently; (6) patients who have signed the informed
17 consent.
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25 Exclusion criteria are as follows: (1) patients with acute meniscus injury, peripheral
26 ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of
27 knee joint, tuberculosis, idiopathic osteonecrosis of the knee; (2) patients with serious
28 cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other
29 hemorrhagic diseases, mental illness, pregnancy and lactation; (3) patients who are
30 allergic or intolerant to trial medication; (4) Patients who had received other treatments
31 in the last 2 months has an effect on the study; (5) patients who are deemed unsuitable
32 for the clinical trial.
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44 **Sample size calculation**

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46 The sample size is calculated with based on a small sample pre-test we carried
47 out in the early stage and the sample size calculation method studied by Bellamy et
48 al.²⁴. The differences between e-WOMAC and p-WOMAC scores were expressed as
49 the mean scores (with standard errors) as 2.95 (5.53). Consequently, with a type I error
50 at 0.05 and type II error at 0.10 considering a 1:1 allocation rate and a drop-out rate of
51 10%, the minimum number of participants needed was 35 per group; a total of 70
52 subjects.
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59 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 Jsurre 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. 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.

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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4 WOMAC will be separately analyzed. All data analysis will be performed
5 by SPSS17.0 statistics software, mean \pm standard deviation (SD) is used to described
6 the metrological data following the normal distribution while median (M) and
7 interquartile range (Q) are used to described the data not following the normal
8 distribution.
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13 First, two conditions will be compared at baseline with a between-group analysis
14 via a t-test in order to ensure there is no difference between randomization groups.
15 To test our hypothesis, in the first stage calculate difference scores of each participant
16 (difference $d = \text{paper WOMAC score} - \text{electronic WOMAC score}$) and the data will be
17 analyzed for normality by the Shapiro-Wilks test. For the primary outcomes we will
18 use the total WOMAC score directly, while for the secondary outcomes
19 WOMAC subscale scores will be rescaled to a 0-100 scale before calculation. A
20 paired t-test will be used to calculate the mean score difference if data is normally
21 distributed, and the results will be reported as 95% confidence intervals between
22 differences in means, if not, Wilcoxon rank-sum test will be used. Two factor ANOVA
23 model will be used to account for any differences due to the order of completing the
24 paper and electronic WOMAC index. In the third stage, the same statistical analysis
25 will be performed after the intervention the same as the first stage in order to investigate
26 whether the WOMAC score of both high and low levels of KOA has good consistency.
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41 To test the consistency of two versions of the WOMAC, an allowed range is
42 defined (i.e. a value for the mean difference that needed to be exceeded to determine
43 that the two WOMACs are not equivalent). As there is great inter-individual variability
44 between different patients, a limit of equivalence will be determined based on the
45 outcome measure of the pre-experiment to provide a strict test of the equivalence of
46 two WOMACs. If the mean (and its 95% confidence interval) of the difference falls
47 within the allowable ranges, then we can gain the credible evidence of equivalence of
48 scoring system of the WOMAC.
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56 Answers to open-ended questions will be subjected to a simple content analysis,
57 categorized as positive, negative, or neutral comments on the e-WOMAC or p-
58 WOMAC.
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4 For the condition of shedding samples that may occur in the current study, we will
5 have strict criterion and the statistical analysis will only include patients who participate
6 in the whole process of the study from enrollment to post-intervention assessment.
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10 11 **Data monitoring**

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14 An external data monitoring committee was not deemed to be necessary for this
15 trial. Data will be monitored by the research team which includes clinicians,
16 statisticians and information technology experts. This study is considered to be a low-
17 risk trial where both the intervention and control groups will receive their usual medical
18 care. The expected duration of the trial lasts only 1 month and the use of the application
19 does not present with high risk, there won't be any stopping guidelines to terminate the
20 trial nor interim analysis planned.
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30 31 **Patient and public involvement**

32 This research is planned to be done without patient involvement. The patients will
33 not be invited to comment on the study design or be consulted on developing patient-
34 relevant outcomes. The future manuscript will not be edited by patients for readability
35 or accuracy.
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40 41 **Discussion**

42 Since KOA is characterized by chronic progressive degeneration of articular
43 cartilage, its assessment involves a complex process and requires an overall evaluation
44 of the patients' condition for a better clinical outcome. However today in China, many
45 residents don't have the access to family doctors, so they usually need to go to hospital
46 for treatment. The inconvenience in visiting doctors may cause delay in treatment.
47 Smartphone application for electronic data capture appears to be an innovative and
48 promising alternative to the original assessment methods as smartphone application
49 have already been proved to be accurate tools.
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58 However, it would be unwise to consider transforming a traditional paper-based
59 patient-reported outcomes measure to an electronic version for use in the clinical
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4 practice and research if the equivalence of the two versions hasn't been proved. In this
5 study protocol, we describe an unblinded trial designed to test a newly developed
6 technology-based KOA assessment consisting of a mobile phone application for
7 patients, which is linked to the physicians. Specifically, we want to explore the
8 reliability and comparability of electronic and paper versions of the WOMAC and
9 whether EDC can help improve treatment adherence by meeting patients' preferences.
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15 To the best of our knowledge, this is the first study to test the reliability of the
16 Chinese electronic WOMAC for KOA assessment. If our hypothesis is confirmed, the
17 findings will serve to demonstrate the equivalence of electronic and paper versions of
18 WOMAC and patients' acceptance of Chinese e-WOMAC so that it can be
19 implemented in clinical practice and research. Likewise, our results will further
20 demonstrate the feasibility of e-health for the personalized KOA therapy. (i.e.
21 timely adjustment of the treatment plan can be rapidly given patients based on self-
22 reported ePRO with the help of smartphone application)
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31 We anticipate that with the support of EDC, physicians will be able to receive
32 timely feedback on patients' conditions, which will significantly improve the
33 visiting rate and treatment rate due to the convenience of telemedicine and rapid
34 response to unwanted events. Note that KOA is a common chronic disease in the elderly,
35 the study will explore the feasibility of enabling the Chinese e-WOMAC for patients'
36 long-term use.
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42 However, using EDC systems may still have some limitations. The degree
43 of familiarity with the electronics is not entirely consistent between different
44 population, especially considering the factors of age, social status and other general
45 factors. For example, some patients who don't have communication vehicles or cannot
46 permit proper use of the application may be excluded from online medical service. In
47 addition, psychological factors may have a relevant influence on filling
48 out the questionnaire leading to the condition that patients feel non-adapted, have
49 difficulty in using the smartphone or even failed to complete the questionnaire.^{26 19}
50 Accordingly, we can make some necessary adjustments of the application. In sum, the
51 results of the present investigation may help to find new ways of developing
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4 smartphone application and information and communication technology in the medical
5 field.
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8 9 **Data management and oversight**

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11 In order to ensure protocol compliance, proper study management, and timely
12 completion of study procedures, members of the research team from Shuguang Hospital
13 Affiliated to Shanghai University of Traditional Chinese Medicine will take
14 responsibility for the conduct of all research staff and study participants.
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19 20 **Protocol and registration**

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22 The trial is registered with the ChiCTR, ChiCTR2100050914. Registered on 8 Sep 2021,
23 <https://www.chictr.org.cn/showproj.aspx?proj=133521>
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29 30 **Data storage security and patient confidentiality**

31 Patients' medical records (descriptive characteristics like name initials, allocated study
32 number, sex, age, BMI, outcome measures like primary outcomes and secondary
33 outcomes and laboratory results) will be kept in the respective hospital, and physicians
34 will document the findings of the study in it, allowing
35 researchers and ethics committees to access the data. Personal information of patients
36 will not be revealed in the results of this study, and we will try everything we
37 can to protect patients' privacy and medical data within the Chinese law. According to
38 medical research ethics, experimental data especially personal privacy information will
39 not be allowed to be accessed and shared by the public and will be limited to web-based
40 databases to ensure that personal privacy information is not disclosed.
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51 52 **Ethics and dissemination**

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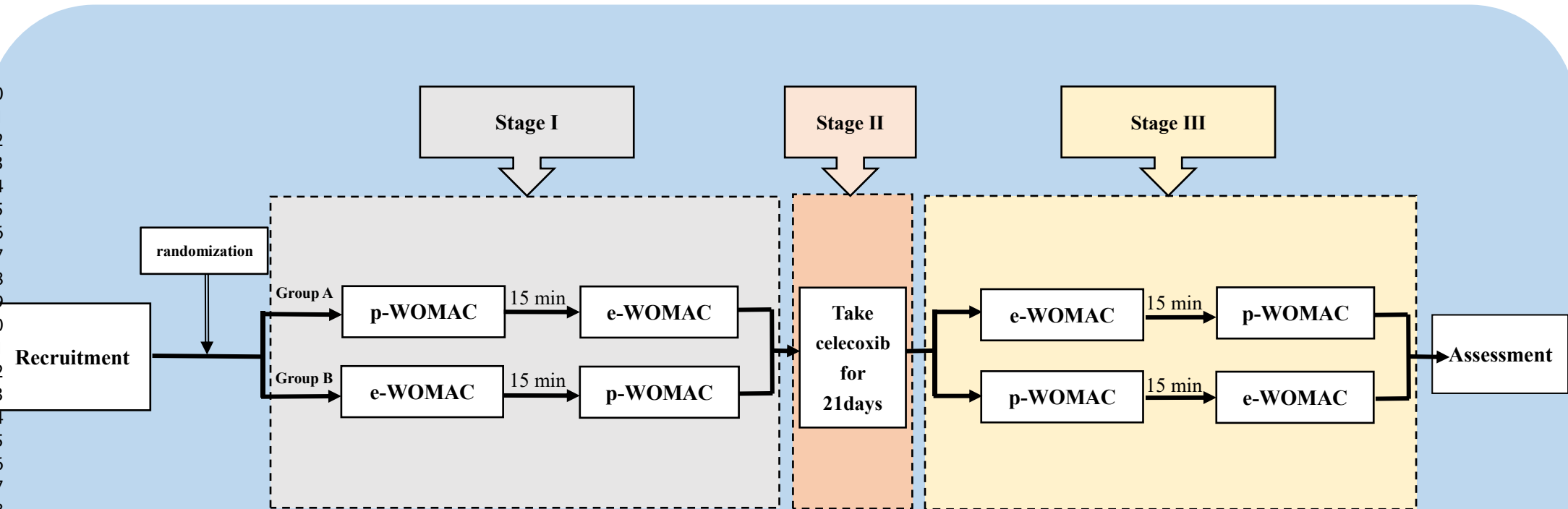


Fig. 1 Flow chart of the study

ePData

点击按钮进入应用

开始

您的医生已经选择了您的研究关节，如果您确定不了哪一处才是您的研究关节，请在填写本调查表以前询问清楚。

您不舒服的地方？

左膝 右膝 双膝

返回

下一步

请根据您在过去48小时内感觉到的膝关节【疼痛程度】将下方的三角滑块滑到合适的位置。

(2) 上楼梯或下楼梯



上一步

下一步

(a)

(b)

(c)

- 1 首页
- 2 报表
- 3 受试者数据
- 4 管理
- 5 患者
- 6 我注册
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数据列表 (中心编号:01)

数据列表 受试者列表

日志填写完成开始时间 日志填写完成结束时间 全部状态 全部受试者编号 全部数据

搜索

受试者编号	日志填写完成时间	日志名称	上传时间	最近修改时间	阶段	状态	操作
S01004	2021-09-26 17:08:52 (UTC+08:00)	问卷评估	2021-09-26 17:08:52 (UTC+08:00)	2021-09-26 17:08:52 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:50:58 (UTC+08:00)	问卷评估	2021-07-21 19:50:58 (UTC+08:00)	2021-07-21 19:50:58 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:48:50 (UTC+08:00)	问卷评估	2021-07-21 19:48:50 (UTC+08:00)	2021-07-21 19:48:50 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:47:33 (UTC+08:00)	问卷评估	2021-07-21 19:47:33 (UTC+08:00)	2021-07-21 19:47:33 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:47:04 (UTC+08:00)	问卷评估	2021-07-21 19:47:04 (UTC+08:00)	2021-07-21 19:47:04 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:46:33 (UTC+08:00)	问卷评估	2021-07-21 19:46:33 (UTC+08:00)	2021-07-21 19:46:33 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:45:45 (UTC+08:00)	问卷评估	2021-07-21 19:45:45 (UTC+08:00)	2021-07-21 19:45:45 (UTC+08:00)	治疗期	有效	操作

(a)

日志详情

受试者编号: S01004

日志名称: 问卷评估

日志填写完成时间: 2021-06-10 20:23:15 (UTC+08:00)

日志上传时间: 2021-06-10 20:23:15 (UTC+08:00)

最近修改时间: 2021-06-10 20:23:15 (UTC+08:00)

阶段: 治疗期

状态: 有效

您不舒服的地方?

左膝:

疼痛程度: (1) 在平坦的路上行走 63;

疼痛程度: (2) 上楼梯或下楼梯 65;

疼痛程度: (3) 晚上,在床上时,就是说打扰您睡觉的疼痛 60;

疼痛程度: (4) 弯腰时 71;

23	行动障碍的程度: (23) 做繁重的家务活问题 54;
24	行动障碍的程度: (24) 做轻松的家务活 48;
25	疼痛评分 294;
26	僵硬评分 140;
27	功能评分 1027;
28	womac总评分 1461;

(b)

(c)

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

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;

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

③ KL classification \leq 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

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.

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.

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

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.

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.: _____



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

Section/item	Item No	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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2		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.
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16		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.
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31	Introduction			Page2 Line16
32				
33	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
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44		6b	Explanation for choice of comparators	n/a There is not a control group in this study.
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47	Objectives	7	Specific objectives or hypotheses	Page4 Line22
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50	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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2 **Methods: Participants, interventions, and**
3 **outcomes**
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5	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
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14	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
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25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page6 Line15
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32		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
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43		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page9 Line17
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51		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page9 Line4
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2	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
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21	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
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31	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
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41	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page6 Line4
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2 Sequence 16a Method of generating the Page6 Line11
3 generation allocation sequence (eg,
4 computer-generated
5 random numbers), and list
6 of any factors for
7 stratification. To reduce
8 predictability of a random
9 sequence, details of any
10 planned restriction (eg,
11 blocking) should be
12 provided in a separate
13 document that is
14 unavailable to those who
15 enrol participants or assign
16 interventions
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21 Allocation 16b Mechanism of implementing Page6 Line12
22 concealme the allocation sequence
23 nt (eg, central telephone;
24 mechanism sequentially numbered,
25 opaque, sealed envelopes),
26 describing any steps to
27 conceal the sequence until
28 interventions are assigned
29
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32 Implement 16c Who will generate the Page6 Line13
33 ation allocation sequence, who
34 will enrol participants, and
35 who will assign participants
36 to interventions
37
38

39 Blinding 17a Who will be blinded after Page7 Line3
40 (masking) assignment to interventions
41 (eg, trial participants, care
42 providers, outcome
43 assessors, data analysts),
44 and how
45

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47 17b If blinded, circumstances n/a Blinding method will
48 under which unblinding is not be used in this study.
49 permissible, and procedure
50 for revealing a participant's
51 allocated intervention
52 during the trial
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55 **Methods: Data collection, management, and**
56 **analysis**
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2	Data	18a	Plans for assessment and	Page10 Line14
3	collection		collection of outcome,	
4	methods		baseline, and other trial	
5			data, including any related	
6			processes to promote data	
7			quality (eg, duplicate	
8			measurements, training of	
9			assessors) and a	
10			description of study	
11			instruments (eg,	
12			questionnaires, laboratory	
13			tests) along with their	
14			reliability and validity, if	
15			known. Reference to where	
16			data collection forms can	
17			be found, if not in the	
18			protocol	
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24		18b	Plans to promote	Page10 Line17
25			participant retention and	
26			complete follow-up,	
27			including list of any	
28			outcome data to be	
29			collected for participants	
30			who discontinue or deviate	
31			from intervention protocols	
32				
33				
34	Data	19	Plans for data entry,	Page10 Line16
35	management		coding, security, and	
36			storage, including any	
37			related processes to	
38			promote data quality (eg,	
39			double data entry; range	
40			checks for data values).	
41			Reference to where details	
42			of data management	
43			procedures can be found, if	
44			not in the protocol	
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49	Statistical	20a	Statistical methods for	Page10 Line20
50	methods		analysing primary and	
51			secondary outcomes.	
52			Reference to where other	
53			details of the statistical	
54			analysis plan can be found,	
55			if not in the protocol	
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2 20b Methods for any additional Page8 Line29
3 analyses (eg, subgroup and
4 adjusted analyses)
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6 20c Definition of analysis n/a Considering the
7 population relating to purpose of this study,
8 protocol non-adherence the data of subjects with
9 (eg, as randomised complete efficacy data
10 analysis), and any before and after
11 statistical methods to treatment will be
12 handle missing data (eg, included in the statistical
13 multiple imputation) analysis.
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17 **Methods: Monitoring**

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19 Data 21a Composition of data Page12 Line13
20 monitoring committee
21 (DMC); summary of its role
22 and reporting structure;
23 statement of whether it is
24 independent from the
25 sponsor and competing
26 interests; and reference to
27 where further details about
28 its charter can be found, if
29 not in the protocol.
30 Alternatively, an
31 explanation of why a DMC
32 is not needed
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37 21b Description of any interim Page12 Line17
38 analyses and stopping
39 guidelines, including who
40 will have access to these
41 interim results and make
42 the final decision to
43 terminate the trial
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45

46 Harms 22 Plans for collecting, Page9 Line16
47 assessing, reporting, and
48 managing solicited and
49 spontaneously reported
50 adverse events and other
51 unintended effects of trial
52 interventions or trial
53 conduct
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2	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.
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10	Ethics and dissemination			
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12	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page14 Line24
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19	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a The preliminary experiments of this research group and the similar types of research by others have proved the feasibility of the research.
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32	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
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39		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.
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47	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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2	Declaration of	28	Financial and other	Page16 Line16
3	interests		competing interests for	
4			principal investigators for	
5			the overall trial and each	
6			study site	
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8				
9	Access to	29	Statement of who will have	Page14 Line28
10	data		access to the final trial	
11			dataset, and disclosure of	
12			contractual agreements that	
13			limit such access for	
14			investigators	
15				
16				
17	Ancillary and	30	Provisions, if any, for	Page9 Line17
18	post-trial care		ancillary and post-trial care,	
19			and for compensation to	
20			those who suffer harm from	
21			trial participation	
22				
23				
24	Dissemination	31a	Plans for investigators and	Page16 Line23
25	policy		sponsor to communicate	
26			trial results to participants,	
27			healthcare professionals,	
28			the public, and other	
29			relevant groups (eg, via	
30			publication, reporting in	
31			results databases, or other	
32			data sharing	
33			arrangements), including	
34			any publication restrictions	
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38		31b	Authorship eligibility	Page16 Line25
39			guidelines and any	
40			intended use of	
41			professional writers	
42				
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44		31c	Plans, if any, for granting	Page16 Line23
45			public access to the full	
46			protocol, participant-level	
47			dataset, and statistical code	
48				
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50	Appendices			
51				
52	Informed	32	Model consent form and	See
53	consent		other related	supplement
54	materials		documentation given to	material
55			participants and authorised	
56			surrogates	
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2	Biological	33	Plans for collection,	n/a This experiment does
3	specimens		laboratory evaluation, and	not involve biological
4			storage of biological	specimens.
5			specimens for genetic or	
6			molecular analysis in the	
7			current trial and for future	
8			use in ancillary studies, if	
9			applicable	
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12 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
13 Explanation & Elaboration for important clarification on the items. Amendments to the
14 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
15 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
16 license.
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-063576.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Aug-2022
Complete List of Authors:	Zhang, yujie; Shuguang Hospital Zhao, ye; Shuguang Hospital Liu, kaoqiang; Shuguang Hospital Chai, yongli; Shuguang Hospital Lin, fen; Shanghai Jsre Health Co., Ltd Zhan, Hongsheng; Shuguang Hospital Zheng, Yuxin; Shuguang Hospital Yuan, Weian; Shuguang Hospital,
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Health services research, Research methods
Keywords:	Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PRIMARY CARE

SCHOLARONE™
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

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2
3
4 The study approach and design enable a comprehensive analysis of the reliability
5 and comparability of paper-based and Chinese electronic version of WOMAC in
6 normal clinical practice in a Chinese population.
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10 This study is a randomized, crossover design with intervention that can verify
11 whether e-WOMAC is the same as p-WOMAC in sensitively reflecting the actual
12 changes in patients' conditions.
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16 In this study, patient satisfaction was added as an outcome to investigate
17 subjects' propensity for paper-based or Chinese electronic version of WOMAC.
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20 As the instruments will be collected using electronic tablets, a certain level of
21 computer literacy is required, and the study may not be able to include participants who
22 are not capable of handling the devices.
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26 Since the patients with KL classification \leq grade 3 KOA were included in the
27 study, the results will not be valid for severe KOA patients.
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33 **Introduction**

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35 Knee osteoarthritis (KOA) is the most common chronic, progressive and
36 degenerative joint disease in middle and old age. It is characterized by articular cartilage
37 degeneration, osteosclerosis and hyperplasia.¹ Major clinical manifestations of KOA
38 include progressive knee joint pain, swelling, stiffness, dysfunction, severe deformation
39 of joints, and even loss of joint function. KOA can lead to pain and dysfunction of the
40 lower limb and affect patients' normal life and work.²
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47 The worldwide prevalence of KOA is increasing, reported to be between 3.8% in
48 2010, and with an estimated 25,000 people suffer from KOA in 2018.^{3 4} There is
49 radiographic evidence of knee osteoarthritis in up to 14% of asymptomatic uninjured
50 adults aged <40 years and 43% of the middle-aged population.⁵ In China,
51 approximately 8.1% of Chinese people are affected by KOA.⁶ KOA can greatly affect
52 the patient's health and quality of life. Today, its incidence tends to increase with
53 the advent of an aging society.⁷ With increased focus on health, people are becoming
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4 more aware of the need for early diagnosis, timely intervention, minimal damage and
5 better prognosis. Patient-reported outcomes (PRO) can truly reflect patients' health
6 status and treatment outcomes, and have played a significant part in the diagnosis and
7 treatment of chronic progressive diseases. The Western Ontario and McMaster
8 University osteoarthritis (WOMAC) index invented by Bellamy is a specific PRO scale,
9 which has high reliability and sensitivity for KOA severity assessment and can
10 accurately reflect the patient's symptoms and functional limitations, and it is also less
11 affected by subjective factors of the patients.⁸ For those who have mild symptoms of
12 OA, it shows high reliability and is currently the most widely used tool to assess the
13 severity level of KOA.⁹

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

48 The visual analogue scale (VAS) is used in e-WOMAC for the assessment of
49 KOA. Pain, stiffness and dysfunction assessment can be completed directly at any time
50 at home through e-WOMAC application, and then physicians can rapidly
51 understand the patient's condition and adapt treatment to achieve
52 personalized healthcare by telemedicine.¹⁵ The main advantages of the e-WOMAC
53 include high efficiency, lower data collection error rate, faster response and
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4 increased response rates.^{16 17 18 19} Practically, online medical service is potentially
5 beneficial for patients with KOA: electronic questionnaire can be completed
6 almost anytime and anyplace, alleviating the influence of environmental factors. The
7 online medical models of care also avoid multiple visits to the clinic. Additionally,
8 paper-less records reduce the waste of resources, which is
9 beneficial for the environment.
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15 Before being put into use, many countries, including the UK, Australia,
16 Switzerland and Austria, have demonstrated the reliability of the e-WOMAC because
17 the difference in MOA may induce bias, even when the index is consistent across modes.
18 R.Theiler argues that English e-WOMAC has similar responsiveness in detecting
19 clinically meaningful change to the traditional p-WOMAC.²⁰ HA Bischoff-Ferrari
20 makes a similar point in his study of consistency between German e-WOMAC with the
21 original format as well.²¹ Similarly, R.Theiler found that the Swiss computerized
22 WOMAC 3.1 and conventional p-WOMAC are similar in all three subscales.²² Overall,
23 these studies illustrate the point that electronic MOA is a promising alternative to the
24 traditional mode.
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35 In China, the existing body of research on the Chinese paper-based WOMAC
36 numerical rating scale (NRS) 3.1 suggests its psychological robustness in reliability and
37 validity.²³ The research also shows that compared with the Lysholm score, IKDC
38 score, HSS score, KSS score and other scales used in the assessment of KOA, Chinese
39 WOMAC 3.1 is the most suitable assessment scale. However, the Chinese electronic
40 WOMAC hasn't been put into use, so research to date has not yet determined the
41 equivalence of Chinese e-WOMAC and the traditional p-WOMAC.
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50 **Objective**

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52 By this research, we aim to evaluate the electronic mode of administration and
53 provide conclusive evidence for developing patient-centered online health applications.
54 We hypothesize that the equivalent between two formats of the WOMAC will be
55 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 [Table 1](#). 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	T ₁	T ₂
	Pre-intervention	Between assessments	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 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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4 each patient at 15 minutes apart in the first and third stage. This study has been
5 registered in Chinese Clinical Trial Registry (ChiCTR2100050914) and will be
6 conducted in strict accordance with Chinese ethical laws and regulations.
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10 **Blinding**

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

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22 Inclusion criteria are as follows: (1) patients who meet the KOA diagnostic criteria
23 of Osteoarthritis Diagnosis and Treatment Guidelines (2018 edition) issued by the Joint
24 Surgery Group of the Orthopaedic Society of the Chinese Medical Association; (2)
25 patients aged 40 to 70 years, including 40 and 70 years, male or female; (3) KL
26 classification \leq grade 3; (4) patients who have a mobile phone and can use the
27 application proficiently; (5) patients who understand Chinese language and can
28 complete the WOMAC independently; (6) patients who have signed the informed
29 consent.
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38 Exclusion criteria are as follows: (1) patients with acute meniscus injury, peripheral
39 ligament rupture injury, rheumatic arthritis, rheumatoid arthritis, peripheral tumor of
40 knee joint, tuberculosis, idiopathic osteonecrosis of the knee; (2) patients with serious
41 cardiovascular, lung, liver, kidney and hematopoietic diseases, hemophilia and other
42 hemorrhagic diseases, mental illness, pregnancy and lactation; (3) patients who are
43 allergic or intolerant to trial medication; (4) Patients who had received other treatments
44 in the last two months has an effect on the study; (5) patients who are deemed unsuitable
45 for the clinical trial.
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56 **Sample size calculation**

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

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

14 15 16 17 18 **Instrument**

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20 WOMAC is a widely used self-administered evaluation tool, which can be
21 completed within 5-10 minutes. Research shows that this scale has objective reliability,
22 effectiveness and sensitivity for evaluation of the knee joint, and it is an evaluation
23 scale that has been widely used for patients with OA. The WOMAC rating scale
24 assesses the structure and function of the hip and knee in terms of pain, stiffness, and
25 joint function. There are 24 items in all covering the basic symptoms and signs of OA,
26 5 items for the pain part, 2 items for the stiffness part, and 17 items for the joint function
27 part, among which each item has a scale bar without a scale line, representing the range
28 of 0-10 points, the starting point on the left side of the scale is 0 point, representing
29 none, and the end point on the right side is 10 points, representing extreme severity.²⁵
30 The regular paper-based WOMAC requires the patient to fill out based on his or her
31 symptoms and signs within 48 hours, which is then measured by a physician based on
32 the location. E-WOMAC, a Chinese-language electronic scale for self-assessment of
33 patients with KOA, used in the study was developed by Shanghai Jsurre Health Co. The
34 text portion of e-WOMAC is identical to WOMAC VAS 3.1. For the first time, the
35 patient needs to scan the QR code and download the Epdata software. After registration
36 and login, patients can fill in the electronic version of WOMAC (figure.2), swipe the
37 ruler on the screen according to their symptoms and signs within 48 hours, and submit
38 after completing the answers. Doctors can directly receive the score data of patients in
39 the Epdata database (figure.3).
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Additional Questions

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4 At the end of the study, a simple questionnaire has been designed to investigate
5 subjects' perceptions of the study and the propensity for the paper-based or electronic
6 version of WOMAC. The questions will involve the description of the advantages and
7 disadvantages of two WOMACs.
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11 12 13 **Interventions**

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

51 The primary outcome of the current study is the mean score difference in
52 WOMAC. This method has been found to be a semi-quantitative rating scale with better
53 reliability and validity and more balanced empirical evidence.¹⁸ The Chinese e-
54 WOMAC, which contains 24 different items split up into 3 subscales: pain subscale (5
55 items), stiffness subscale (2 items), and physical function subscale (17 items) will be
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4 asked to patients. Primary outcomes will be analyzed and reported in two ways. First,
5 we will compare the difference in the respective score of e-WOMAC and p-WOMAC
6 before and after the intervention. Then, we will investigate patients' acceptance of two
7 forms of the WOMAC through a simple self-made questionnaire.
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11 12 13 **Secondary outcomes**

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

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32 We will gather information at every stage of recruitment, randomization and
33 treatment so that we can report flow of patients according to the CONSORT guidelines.
34 Once a subject is enrolled or randomized, the study site will make every reasonable
35 effort to follow the subject for the entire study period. Considering the purpose of this
36 study, the data of subjects with complete efficacy data before and after treatment will
37 be included in the statistical analysis.
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44 The paper questionnaire will be completed by subjects alone, and data will be
45 collected by trained investigators, then reach the database. The electronic questionnaire
46 will be completed by subjects alone via the smartphone application. The score of e-
47 WOMAC will be entered into an excel file and then analyzed by SPSS. Note that time
48 intervals between two assessments should be 15 minutes in order to eliminate the
49 influence of memory and maintain data quality and objectivity.
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58 **Statistical analysis**

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

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 \pm 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 $d = \text{paper WOMAC score} - \text{electronic WOMAC score}$) 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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4 two WOMACs. If the mean (and its 95% confidence interval) of the difference falls
5 within the allowable ranges, then we can gain credible evidence of the equivalence of
6 the scoring system of the WOMAC.
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10 Answers to open-ended questions will be subjected to a simple content analysis,
11 categorized as positive, negative, or neutral comments on the e-WOMAC or p-
12 WOMAC.
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15 For the condition of shedding samples that may occur in the current study, we will
16 have strict criterion and the statistical analysis will only include patients who participate
17 in the whole process of the study from enrollment to post-intervention assessment.
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23 **Data monitoring**

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

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

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52 Since KOA is characterized by chronic progressive degeneration of articular
53 cartilage, its assessment involves a complex process and requires an overall evaluation
54 of the patient's condition for a better clinical outcome. However, today in China, many
55 residents don't have access to family doctors, so they usually need to go to hospital for
56 treatment. The inconvenience of visiting doctors may cause delay in treatment.
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4 Smartphone application for electronic data capture appears to be an innovative and
5 promising alternative to the original assessment methods, as smartphone application
6 have already been proved to be accurate tools.
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10 However, it would be unwise to consider transforming a traditional paper-based
11 patient-reported outcomes measure to an electronic version for use in clinical practice
12 and research if the equivalence of the two versions hasn't been proved. In this study
13 protocol, we describe an unblinded trial designed to test a newly developed technology-
14 based KOA assessment consisting of a mobile phone application for patients, which is
15 linked to the physicians. Specifically, we want to explore the reliability and
16 comparability of electronic and paper versions of the WOMAC and whether electronic
17 MOA can help improve treatment adherence by meeting patients' preferences.
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25 To the best of our knowledge, this is the first study to test the reliability of the
26 Chinese electronic WOMAC for KOA assessment. If our hypothesis is confirmed, the
27 findings will serve to demonstrate the equivalence of electronic and paper versions of
28 WOMAC and patients' acceptance of Chinese e-WOMAC so that it can be
29 implemented in clinical practice and research. Likewise, our results will further
30 demonstrate the feasibility of e-health for personalized KOA therapy. (i.e.,
31 timely adjustment of the treatment plan can be rapidly given to patients based on self-
32 reported ePRO with the help of a smartphone application)
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41 We anticipate that with the support of electronic MOA, physicians will be able to
42 receive timely feedback on patients' conditions, which will significantly improve the
43 visiting rate and treatment rate due to the convenience of telemedicine and rapid
44 response to unwanted events. Note that KOA is a common chronic disease in the elderly,
45 the study will explore the feasibility of enabling the Chinese e-WOMAC for patients'
46 long-term use.
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52 However, using EDC systems may still have some limitations. The degree
53 of familiarity with the electronics is not entirely consistent between different
54 populations, especially considering the factors of age, social status and other general
55 factors. For example, some patients who don't have communication vehicles or cannot
56 permit proper use of the application may be excluded from the online medical service.
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4 In addition, psychological factors may have a relevant influence on filling
5 out the questionnaire leading to the condition that patients feel non-adapted, have
6 difficulty in using the smartphone or even fail to complete the questionnaire.²⁶
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8 Accordingly, we can make some necessary adjustments to the application. In sum, the
9 results of the present investigation may help to find new ways of developing
10 smartphone applications and information and communication technology in the
11 medical field. In addition, it will also be more favorable to select the most appropriate
12 MOA for PROs, including electronic MOA, paper-based MOA or mixed-mode designs.
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21 **Data management and oversight**

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

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35 The trial is registered with the ChiCTR, ChiCTR2100050914. Registered on 8 Sep 2021,
36 <https://www.chictr.org.cn/showproj.aspx?proj=133521>
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41 **Data storage security and patient confidentiality**

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43 Patient's medical records (descriptive characteristics like name initials, allocated study
44 number, sex, age, BMI, outcome measures like primary outcomes and secondary
45 outcomes and laboratory results) will be kept in the respective hospital, and physicians
46 will document the findings of the study in it, allowing
47 researchers and ethics committees to access the data. Personal information of patients
48 will not be revealed in the results of this study, and we will try everything we
49 can to protect patients' privacy and medical data within Chinese law. According to
50 medical research ethics, experimental data, especially personal privacy information,
51 will not be allowed to be accessed and shared by the public and will be limited to web-
52 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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11 disease clinical medical research center (20MC1920600).
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16 **Disclaimer**

17 The funding organization has not played any role in the design and conduct of the study;
18 collection, management, analysis, or interpretation of the data; or preparation of the
19 manuscript.
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23 **Competing interests**

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

31 Not required
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33 **Availability of data and material**

34 The datasets analyzed during the current study will be available from the corresponding
35 author on reasonable request.
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39 **Consent for publication**

40 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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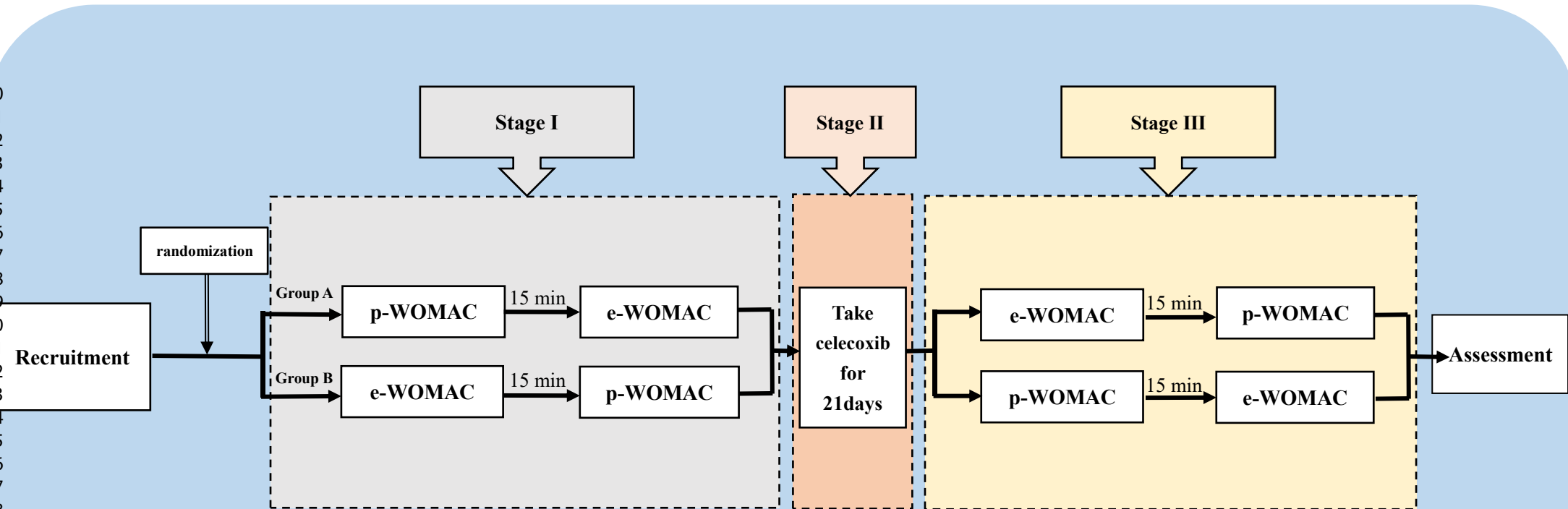


Fig. 1 Flow chart of the study

ePData

点击按钮进入应用

开始

您的医生已经选择了您的研究关节，如果您确定不了哪一处才是您的研究关节，请在填写本调查表以前询问清楚。

您不舒服的地方？

左膝 右膝 双膝

返回

下一步

请根据您在过去48小时内感觉到的膝关节【疼痛程度】将下方的三角滑块滑到合适的位置。

(2) 上楼梯或下楼梯

无疼痛感 极度疼痛

(a)

(b)

(c)

- 1 首页
- 2 报表
- 3 受试者数据
- 4 管理
- 5 流程
- 6 我注册
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数据列表 (中心编号:01)

数据列表 受试者列表

日志填写完成开始时间 日志填写完成结束时间 全部状态 全部受试者编号 全部数据

搜索

受试者编号	日志填写完成时间	日志名称	上传时间	最近修改时间	阶段	状态	操作
S01004	2021-09-26 17:08:52 (UTC+08:00)	问卷评估	2021-09-26 17:08:52 (UTC+08:00)	2021-09-26 17:08:52 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:50:58 (UTC+08:00)	问卷评估	2021-07-21 19:50:58 (UTC+08:00)	2021-07-21 19:50:58 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:48:50 (UTC+08:00)	问卷评估	2021-07-21 19:48:50 (UTC+08:00)	2021-07-21 19:48:50 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:47:33 (UTC+08:00)	问卷评估	2021-07-21 19:47:33 (UTC+08:00)	2021-07-21 19:47:33 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:47:04 (UTC+08:00)	问卷评估	2021-07-21 19:47:04 (UTC+08:00)	2021-07-21 19:47:04 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:46:33 (UTC+08:00)	问卷评估	2021-07-21 19:46:33 (UTC+08:00)	2021-07-21 19:46:33 (UTC+08:00)	治疗期	有效	操作
S01004	2021-07-21 19:45:45 (UTC+08:00)	问卷评估	2021-07-21 19:45:45 (UTC+08:00)	2021-07-21 19:45:45 (UTC+08:00)	治疗期	有效	操作

(a)

日志详情

受试者编号: S01004

日志名称: 问卷评估

日志填写完成时间: 2021-06-10 20:23:15 (UTC+08:00)

日志上传时间: 2021-06-10 20:23:15 (UTC+08:00)

最近修改时间: 2021-06-10 20:23:15 (UTC+08:00)

阶段: 治疗期

状态: 有效

您不舒服的地方?

左膝:

疼痛程度: (1) 在平坦的路上行走 63;

疼痛程度: (2) 上楼梯或下楼梯 65;

疼痛程度: (3) 晚上,在床上时,就是说打扰您睡觉的疼痛 60;

疼痛程度: (4) 弯腰时 71;

23	行动障碍的程度: (23) 做繁重的家务活问题 54;
24	行动障碍的程度: (24) 做轻松的家务活 48;
25	疼痛评分 294;
26	僵硬评分 140;
27	功能评分 1027;
28	womac总评分 1461;

(b)

(c)

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

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;

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

③ KL classification \leq 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

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.

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.

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

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

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

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

11 If you do not participate in this study, your research physician will provide you with
12 alternative treatment options, such as other drug or exercise therapies for knee osteoarthritis.
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15 16 **What should you do at the present time?**

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

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

25 Ethics Committee Office: The second floor of the eastern administration of Shuguang
26 Hospital
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28 Tel.: 20256070
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31 Thank you for reading the above material. If you decide to participate in this study, tell your
32 doctor and he/she will arrange everything for you to do with the study.
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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.: _____



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

Section/item	Item No	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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2		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.
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16		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.
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31	Introduction			Page2 Line16
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33	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
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44		6b	Explanation for choice of comparators	n/a There is not a control group in this study.
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47	Objectives	7	Specific objectives or hypotheses	Page4 Line23
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50	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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2 **Methods: Participants, interventions, and**
3 **outcomes**
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5	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
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14	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
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25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page6 Line19
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32		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
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43		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page9 Line23
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51		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page9 Line10
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2	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
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21	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
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31	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
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41	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page6 Line10
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the	Page6 Line13
3	generation		allocation sequence (eg,	
4			computer-generated	
5			random numbers), and list	
6			of any factors for	
7			stratification. To reduce	
8			predictability of a random	
9			sequence, details of any	
10			planned restriction (eg,	
11			blocking) should be	
12			provided in a separate	
13			document that is	
14			unavailable to those who	
15			enrol participants or assign	
16			interventions	
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21	Allocation	16b	Mechanism of	Page6 Line14
22	concealme		implementing the allocation	
23	nt		sequence (eg, central	
24	mechanism		telephone; sequentially	
25			numbered, opaque, sealed	
26			envelopes), describing any	
27			steps to conceal the	
28			sequence until interventions	
29			are assigned	
30				
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33	Implement	16c	Who will generate the	Page6 Line15
34	ation		allocation sequence, who	
35			will enrol participants, and	
36			who will assign participants	
37			to interventions	
38				
39				
40	Blinding	17a	Who will be blinded after	Page7 Line5
41	(masking)		assignment to interventions	
42			(eg, trial participants, care	
43			providers, outcome	
44			assessors, data analysts),	
45			and how	
46				
47				
48		17b	If blinded, circumstances	n/a Blinding method will
49			under which unblinding is	not be used in this study.
50			permissible, and procedure	
51			for revealing a participant's	
52			allocated intervention	
53			during the trial	
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Methods: Data collection, management, and analysis

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2	Data	18a	Plans for assessment and	Page10 Line25
3	collection		collection of outcome,	
4	methods		baseline, and other trial	
5			data, including any related	
6			processes to promote data	
7			quality (eg, duplicate	
8			measurements, training of	
9			assessors) and a	
10			description of study	
11			instruments (eg,	
12			questionnaires, laboratory	
13			tests) along with their	
14			reliability and validity, if	
15			known. Reference to where	
16			data collection forms can	
17			be found, if not in the	
18			protocol	
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24		18b	Plans to promote	Page10 Line27
25			participant retention and	
26			complete follow-up,	
27			including list of any	
28			outcome data to be	
29			collected for participants	
30			who discontinue or deviate	
31			from intervention protocols	
32				
33				
34	Data	19	Plans for data entry,	Page10 Line24
35	management		coding, security, and	
36			storage, including any	
37			related processes to	
38			promote data quality (eg,	
39			double data entry; range	
40			checks for data values).	
41			Reference to where details	
42			of data management	
43			procedures can be found, if	
44			not in the protocol	
45				
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48				
49	Statistical	20a	Statistical methods for	Page11 Line2
50	methods		analysing primary and	
51			secondary outcomes.	
52			Reference to where other	
53			details of the statistical	
54			analysis plan can be found,	
55			if not in the protocol	
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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

1				
2	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.
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10	Ethics and dissemination			
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12	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page15 Line9
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19	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a The preliminary experiments of this research group and the similar types of research by others have proved the feasibility of the research.
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32	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
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39		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.
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47	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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2	Declaration of	28	Financial and other	Page16 Line26
3	interests		competing interests for	
4			principal investigators for	
5			the overall trial and each	
6			study site	
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8				
9	Access to	29	Statement of who will have	Page15 Line1
10	data		access to the final trial	
11			dataset, and disclosure of	
12			contractual agreements that	
13			limit such access for	
14			investigators	
15				
16				
17	Ancillary and	30	Provisions, if any, for	Page9 Line20
18	post-trial care		ancillary and post-trial care,	
19			and for compensation to	
20			those who suffer harm from	
21			trial participation	
22				
23				
24	Dissemination	31a	Plans for investigators and	Page16 Line33
25	policy		sponsor to communicate	
26			trial results to participants,	
27			healthcare professionals,	
28			the public, and other	
29			relevant groups (eg, via	
30			publication, reporting in	
31			results databases, or other	
32			data sharing	
33			arrangements), including	
34			any publication restrictions	
35				
36				
37				
38		31b	Authorship eligibility	Page16 Line35
39			guidelines and any	
40			intended use of	
41			professional writers	
42				
43				
44		31c	Plans, if any, for granting	Page16 Line33
45			public access to the full	
46			protocol, participant-level	
47			dataset, and statistical code	
48				
49				
50	Appendices			
51				
52	Informed	32	Model consent form and	See
53	consent		other related	supplement
54	materials		documentation given to	material
55			participants and authorised	
56			surrogates	
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2	Biological	33	Plans for collection,	n/a This experiment does
3	specimens		laboratory evaluation, and	not involve biological
4			storage of biological	specimens.
5			specimens for genetic or	
6			molecular analysis in the	
7			current trial and for future	
8			use in ancillary studies, if	
9			applicable	
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12 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
13 Explanation & Elaboration for important clarification on the items. Amendments to the
14 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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