Author’s response to reviews

Title: Autologous cell-derived tissue engineered cartilage for repairing articular cartilage lesions in the knee: study protocol for a randomized controlled trial

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Author’s response to reviews:

Reviewer reports:

AE Report:

Suggestions made following SPIRIT2013 recommendations. While these apply most to drug trials there are some elements that could be applicable to non-pharmacological clinical trials. Within the publication there are worked examples for each item.

Among the most critical items to revise there are the study outcome, study statistics and justification for sample size.

See below comments for each item of spirit 2013
Item 1: Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: please make compliant to spirit2013

Re: This comment is very prudent to elevate the quality of our MS. The title has been changed into “Autologous cell-derived tissue engineered cartilage for repairing articular cartilage lesions in the knee: study protocol for a randomized controlled trial”.

Item 2a: Trial identifier and registry name. If not yet registered, name of intended registry: compliant.

Re: We fully agree with the reviewer’s opinion.

Item 2b: All items from the World Health Organization Trial Registration Data Set: Not applicable

Re: We fully agree with the reviewer’s opinion.

Item 3: Date and version identifier: Not applicable

Re: We fully agree with the reviewer’s opinion.

Item 4: Sources and types of financial, material, and other support: compliant

Re: We fully agree with the reviewer’s opinion.

Item 5a: Names, affiliations, and roles of protocol contributors: compliant

Re: We fully agree with the reviewer’s opinion.

Item 5b: Name and contact information for the trial sponsor: please make compliant to spirit2013

Re: Trial sponsor is Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing, P.R. China 100853.
Corresponding author: Quan-yi Guo (Principal Investigator), doctorguo_301@163.com.

Item 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: please make compliant to spirit2013

Re: The statement of “Funding” was added as follows: “This work was supported by the National Natural Science Foundation of China (81472092), National High Technology Research and Development Program of China (2012AA020502), the Special Grant for the Science and Technology Research of Beijing (Z161100005016059); the National Key R & D Plan of China (2017YFC1104100), the Translational Foundation of PLA General Hospital (2016TM-015), and the Natural Science Foundation of Beijing (7172203). However, these funding agencies will not participate in study design, manuscript preparation, data collection and analysis, and they have no ultimate authority over any of these activities.”

Item 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): item missing

Re: The item was added as follows: “An independent data monitoring committee approved by the PLA General Hospital will be responsible for data monitoring, including protocol violations, recruitment rate, AEs and participant compliance, which has the right to access all the trial data, but with no conflict of interest.”

Item 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: compliant

Re: We fully agree with the reviewer’s opinion.

Item 6b: Explanation for choice of comparators: item missing

Re: This comment is very prudent to elevate the quality of our MS. The following section was added in the Introduction: “Microfracture is an arthroscopic bone marrow stimulation technique first applied in clinical practice by Steadman and Rodrigo in 1985. During microfracture surgery, damaged articular cartilage is cleaned until the edge of the normal
Articular cartilage and subchondral bone marrow cells, chondrocytes and bone cells penetrate into the damaged area through a hole made using an awl on the surface of the exposed subchondral bone. Blood clots seeping out of the hole adhere to surrounding normal cartilage tissues, forming a fibrous cartilage repair defect area responsible for joint function recovery [18]. Arthroscopic microfracture is the most widely used method for the surgical repair of articular cartilage injuries because of its simple operation and satisfactory clinical efficacy [19]. Here, microfracture surgery will be used as a control for the repair of articular cartilage injury.”

Item 7: Specific objectives or hypotheses: please make compliant to spirit2013

Re: The following section was added: “We hypothesized that autologous cell-derived tissue engineered cartilage is superior to microfractures in the treatment of knee cartilage injury.

The main objective of the study is to evaluate the function and symptom recovery in patients with knee joint cartilage injury undergoing autologous cell-derived cartilage treatment and to compare it with microfracture surgery, based on Lysholm scores at 12 months postoperatively as the primary outcome measure.

The secondary objective of the study is to (1) compare the effectiveness of the two repair methods on knee function recovery based on International Knee Documentation Committee (IKDC) scores, (2) compare the effectiveness of the two repair methods on pain relief, (3) assess cartilage regeneration by MRI, and (4) compare the safety of the two repair methods for knee cartilage repair.”

Item 8: Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory): compliant

Re: We appreciate the concern of the reviewer and totally agree with these comments.

Item 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: compliant

Re: We fully agree with the reviewer’s opinion.
Item 10: Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists). Eligibility criteria for surgeons missing

Re: This comment is very prudent to elevate the quality of our MS. “Eligibility criteria for surgeons: (1) attending physicians with more than 10 years of standing and experience; (2) experience of > 200 arthroscopic surgeries per year; and (3) experience and ability to deal with emergencies.” was added.

Item 11a: Interventions for each group with sufficient detail to allow replication, including how and when they will be administered. Control group should be better described

Re: This comment is very prudent to elevate the quality of our MS. As reviewer suggested, the intervention of the control group was described as follows: “Patients in the control group will be subjected to arthroscopic debridement and microfracture surgery. Regional block, intraspinal anesthesia or general anesthesia will be used during surgery. Patients will be restrained in a supine position during arthroscopy, with their affected limb drooped, followed by joint debridement, including joint lavage, synovectomy, treatment of articular cartilage injury, removal of free bodies and osteophytes, meniscus surgery, treatment of intercondylar fossa and anterior cruciate ligament impingement syndrome. After removal of floating cartilage pieces, the joint will be cleaned of calcified bone using a scraper, and tiny fracture holes will drilled outwardly in a rotation manner with an interval of 3–4 mm at the center of the subchondral bone to ensure the leakage of blood and bone marrow (containing some stem cells) from the holes to form blood clots that differentiate into chondrocytes. After surgery, these chondrocytes will gradually become fibrous cartilage components.”

Item 11b: Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease): compliant

Re: We fully agree with the reviewer’s opinion.

Item 11c: Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return; laboratory tests): Not applicable

Re: We fully agree with the reviewer’s opinion.
Item 11d: Relevant concomitant care and interventions that are permitted or prohibited during the trial: missing

Re: This comment is very prudent to elevate the quality of our MS. The corresponding content was added as follows: “Proper rehabilitation and good lifestyle will allow patients to regain their health as soon as possible. The following actions should be avoided to obtain maximum rehabilitation including: sitting on a low bench (about 20 cm in height), using a squattoilet, strenuous exercise, accidental falls, internal and external rotation of the knee joint, and lying on the affected side. After muscle strength training, patients will feel mild muscle soreness. The presence of mild muscle soreness and ligament strain or muscle soreness at the 2nd day after exercise is normal and will lead to strengthened muscles and stabilized joints. However, a rest plus ice compress is necessary if the pain lasts for several days, which indicates excessive exercise. If the knee pain is severe and the patient’s activities are severely limited, patients should see a doctor immediately.”

Item 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: analysis metric, method of aggregation, time point missing. Explanation of the clinical relevance missing. Moreover not clear if and how there will be a combination of objective and subjective evaluations for building primary outcome.

Re: This comment is very prudent to elevate the quality of our MS. As reviewer suggested, this part was revised as follows:

Outcome measures

Primary outcome measure

The Lysholm score for efficacy evaluation will be recorded at 12 months postoperatively. The Lysholm score [20] ranges from 0–100 points and consists of 8 dimensions: a score of 80–100 points indicates elimination of all or the main symptoms, basic recovery of joint function, being capable of participating in normal labor and work (excellent); 60–79 points indicates elimination of all or the main symptoms, basic recovery or great improvement in the main function of the joint (good); and 0–59 points indicates no symptom improvement or symptom deterioration (poor). Efficiency = the number of excellent and good cases/the total number of cases × 100%.
Secondary outcome measures

- Lysholm score at baseline, 3, 6, and 18 months after operation.

- International Knee Documentation Committee (IKDC) score at baseline, 3, 6, 12, and 18 months after operation. The IKDC scores range from 0–100 points and involves symptoms, sport activities, and function, with higher scores reflecting a better condition (knee function and symptoms).

- Visual analog scale (VAS) score at baseline, 3, 6, 12, and 18 months after operation. The VAS is the most commonly used method to assess pain and consists of a 10-cm horizontal line with one end labeled as 0 cm representing the “no pain” and the other end labeled as 10 cm representing “severe pain”. Patients will be instructed to make a mark on the line to indicate their pain intensity. The VAS scores range from 0–10 points, with 0 indicating no pain, 1–3 indicating mild pain, 4–6 indicating moderate pain, and 7–10 indicating severe pain.

- MRI examination to evaluate cartilage repair and regeneration at baseline, 3, 6, 12, and 18 months after operation.

Item 13: Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended: compliant

Re: We fully agree with the reviewer’s opinion.

Item 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: how it was determined, including clinical and statistical assumptions supporting any sample size calculations missing

Re: This comment is very prudent to elevate the quality of our MS. The item of “Based on our previous experience [23] and pilot study results, we assumed that the therapeutic efficiency on full-thickness cartilage injury of the knee joint would be 78% for microfracture surgery and 97% for autologous cell-derived tissue-engineered cartilage transplantation. Considering \( \alpha = 0.05 \) (two-sided), and power = 80%, the necessary sample size was calculated as \( n = 84 \). With a predicted dropout rate of 20%, the required sample size was calculated as \( n = 50 \) per group.”.
Item 15: Strategies for achieving adequate participant enrolment to reach target sample size: missing

Re: This comment is very prudent to elevate the quality of our MS. The item of “patient recruitment” was added as follows: “Patients with full-thickness cartilage injury of the knee joint will be recruited from outpatients and inpatients at the PLA General Hospital. Patients who are interested in participation in the trial can contact the sponsor through their attending physicians via telephone, E-mail, or WeChat. Recruitment information will be issued through hospital websites, social software and posters.”

Item 16a: Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions: please explain which type of randomization will be implemented (e.g. simple randomization, blocked randomization).

Re: This comment is very prudent to elevate the quality of our MS. It was revised as follows: “A randomization sequence table will be generated using SAS 9.1 software (Copyright SAS Institute Inc., Cary, NC, USA) by professional statisticians who will not participate in the trial. Each patient will be randomly assigned a sequence number. The random number will be concealed in sealed envelopes and saved by a researcher who will not participate in the trial. If severe adverse events occur, the researcher will be informed of the need to open the envelope through a Principal Investigator telephone in situations where code break is warranted. After providing informed consent, eligible patients will be assigned randomly. The final unblinding will be done after data collection.”

Item 16b: Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned: compliant

Re: We fully agree with the reviewer’s opinion.

Item 16c: Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions: information missing

Re: This comment is very prudent to elevate the quality of our MS. It was revised as follows: “A randomization sequence table will be generated using SAS 9.1 software (Copyright SAS Institute Inc., Cary, NC, USA) by professional statisticians who will not participate in the trial. Each
patient will be randomly assigned a sequence number. The random number will be concealed in sealed envelopes and saved by a researcher who will not participate in the trial. If severe adverse events occur, the researcher will be informed of the need to open the envelope through a Principal Investigator telephone in situations where code break is warranted. After providing informed consent, eligible patients will be assigned randomly. The final unblinding will be done after data collection.”

Item 17a: Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how: compliant

Re: We fully agree with the reviewer’s opinion.

Item 17b: If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant’s allocated intervention during the trial: not applicable

Re: We fully agree with the reviewer’s opinion.

Item 18a: Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol: compliant

Re: We fully agree with the reviewer’s opinion.

Item 18b: Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: it is explained what will be collected however it looks like there are no plans to promote participant retention and complete follow-up.

Re: This comment is very prudent to elevate the quality of our MS. It was revised to be “Free strategies for referral, physical examination and MRI review will be conducted during the trial to improve patient compliance.

For patients who are out of the group and cannot be replaced or re-enter the clinical trial, their data will be treated as follows. (1) All source data and source files related to all withdrawn participants will be retained for retention and intent-to-treat analysis. After withdrawal, the
researchers will attempt to contact the patient by telephone or mail to ask the reasons for withdrawal. (2) The time and cause of withdrawal will be recorded on the case report form in detail. (3) If there is judged to be a causal relationship with the trial, withdrawal due to adverse events will be recorded in the CRF and the sponsor will be notified. For such patients, follow-up will be conducted until adverse events are resolved or stabilized.”

Item 19: Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol: compliant

Re: We fully agree with the reviewer’s opinion.

Item 20a: Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol: it is not explained how each outcome will be evaluated.

Re: This comment is very prudent to elevate the quality of our MS. The statement of “statistical analysis” was revised to be “Data will be analyzed using SPSS19.0 software (IBM Corp., Armonk, NY, USA). A statistical significance level of 0.05 will be used. Normally distributed data will be expressed as the mean ± standard deviation, and non-normally distributed data will be expressed as the median, minimum, and maximum. Classified variables will be expressed as a number and percentage.

The analysis will be performed on the basis of the intent-to-treat principle. A full analysis set following the principle of intent-to-treat will consist of a data set for all patients who participated in the trial, regardless of compliance or withdrawal. For patients who are lost to follow-up, the missing data will be imputed by the last observation carried forward method based on the final observed value. Descriptive statistics will be used for baseline feature data. Pearson chi-squared test or Fisher’s exact test will be used for intergroup comparisons of categorical variables, such as curative outcomes and postoperative incidence of adverse events. For independent variables, such as IKDC score, VAS score, T2 value andΔR1, an independent sample t-test or Mann-Whitney U-test will be used.

A multivariate logistic regression analysis model will be used to adjust for possible confounding variables such as age, sex, etiology, cartilage defect area, meniscus injury, course of disease, severity of cartilage injury, postoperative complications, and surgeon (experience).”
Item 20b: Methods for any additional analyses (eg, subgroup and adjusted analyses): not clear if such analyses will be performed

Re: This comment is very prudent to elevate the quality of our MS. However, there is no subgroup analysis. The statement of “adjusted analyses” was revised to be “A multivariate logistic regression analysis model will be used to adjust for possible confounding variables such as age, sex, etiology, cartilage defect area, meniscus injury, course of disease, severity of cartilage injury, postoperative complications, and surgeon (experience).”

Item 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): definition of analysis populations and methods to handle missing data missing

Re: This comment is very prudent to elevate the quality of our MS. As reviewers suggested, “A full analysis set following the principle of intent-to-treat will consist of a data set for all patients who participated in the trial, regardless of compliance or withdrawal. For patients who are lost to follow-up, the missing data will be imputed by the last observation carried forward method based on the final observed value.” was added.

Item 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: item missing

Re: This comment is very prudent to elevate the quality of our MS. The statement of “data monitoring” was added as follows: “An independent data monitoring committee approved by the PLA General Hospital will be responsible for data monitoring, including protocol violations, recruitment rate, AEs and participant compliance, which has the right to access all the trial data, but with no conflict of interest.”

Item 21b: Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial: NA

Re: We fully agree with the reviewer’s opinion.
Item 22: Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct: compliant

Re: We fully agree with the reviewer’s opinion.

Item 23: Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor: missing

Re: This comment is very prudent to elevate the quality of our MS. The statement of “Auditing” was added as follows: “An inspector will audit the incoming data monthly and, if necessary, data queries will be raised. The inspector will review whether the eCRF is completed accurately. All discrepancies in the eCRF will be corrected by the researchers or authorized personnel in the appropriate manner.”

Item 24: Plans for seeking research ethics committee/institutional review board (REC/IRB) approval: compliant

Re: We fully agree with the reviewer’s opinion.

Item 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): missing

Re: This comment is very prudent to elevate the quality of our MS. The statement of “protocol amendments” was added as follows: “All protocol modifications must be signed by the sponsor and dated, and then released. The modified protocol will be approved by the ethics committee prior to implementation. No program deviations should happen during the study. If so, appropriate measures should be taken immediately. Causes of a program deviation and its details should be recorded in a case report form and in the original case form. The program deviation table and case report form will be kept in the research unit and by the sponsor, respectively.”

Item 26a: Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how: who will obtain the consent is missing

Re: The corresponding content was stated as follows: “Prior to participation in the clinical trial, the participant or his/her family members, guardians, and/or legal representatives will be
informed of the details of the clinical trial, including known, foreseeable risks and possible adverse events. Then, the informed consent form will be given to the participant or his/her legal representative.”

Item 26b: Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: not applicable

Re: We fully agree with the reviewer’s opinion.

Item 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: compliant

Re: We fully agree with the reviewer’s opinion.

Item 28 Financial and other competing interests for principal investigators for the overall trial and each study site: compliant

Re: We fully agree with the reviewer’s opinion.

Item 29: Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators: item partly compliant. For instance, how will you share the raw images, data (including computer databases) and samples?

Re: This comment is very prudent to elevate the quality of our MS. The following content was added: “The original raw images, data (including computer databases) and samples obtained during the trial will be published as supplementary information in peer-reviewed academic journals and published data will be released at www.figshare.com.”

Item 30: Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation: item missing

Re: This comment is very prudent to elevate the quality of our MS. The following content has been added as required: “The patient as the insured will be indemnified in respect of postoperative complications stated in the schedule during the period of postoperative follow-up,
physical examination and rehabilitation guidance according to the medical accident insurance purchased preoperatively.”

Item 31a: Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication: compliant

Re: We fully agree with the reviewer’s opinion.

Item 31b: Authorship eligibility guidelines and any intended use of professional writers: missing

Re: This comment is very prudent to elevate the quality of our MS. The following content was added as required: “The authors' signatures of the articles published in this study will be based on the author's signature guidelines, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.”

Item 31c: Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code: missing

Re: This comment is very prudent to elevate the quality of our MS. The following content was added as required: “The original raw images, data (including computer databases) and samples obtained during the trial will be published as supplementary information in peer-reviewed academic journals and published data will be released at www.figshare.com. The results of the trial will be disseminated through peer-reviewed publications and presentations at relevant conferences.”

Item 32: Model consent form and other related documentation given to participants and authorised surrogates: Not applicable

Re: We fully agree with the reviewer’s opinion.

Item 33: Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable: not clear if biological specimens will be stored. If yes, please provide a description compliant with this item
Re: Thanks for your suggestions, but we have no relevant description compliant with this item.

Reviewer #1: The protocol presented here is very interesting and its development can produce genuine value and hope for patients with cartilage lesions.

However, before its acceptance and conduction, clearness should be done concerning planning and analysis. The final aim is to get clear interpretations of results and clinical impacts.

I've got a question concerning inclusion criteria: why do you consider an age range of 14-50. Does it mean that intervention can't be considered for older people?

Re: Patients over 50 years of age have poor viability of autologous chondrocytes.

On exclusion criteria: statements as "Poor health", "Blood diseases" are very "large" and unspecific. I suggest to give more precise criteria to avoid biases related to recruitment.

Re: This comment is very prudent to elevate the quality of our MS. It has been detailed as follows:

- Autoimmune diseases (rheumatoid, chronic kidney disease)
- Hematosis (thrombocytopenia, leukaemia)

In the paragraph: "interventions_ Therapeutic approach": when you say "...if the patient's condition meets the surgical requirement, we will extract cartilage from the fossa intercondylar non-weight-bearing area during the first surgery...". If no surgical requirement is met, are patients withdrawn from the study?

Re: This comment is very prudent to elevate the quality of our MS. The corresponding content was stated in the “Withdrawal criteria” section: “the patient fails to meet surgical requirements under arthroscopy will be withdrawn from the study.”

I don't understand what the Primary Endpoint exactly is. You use objective and subjective evaluations: do you analyze it separately? Do you use a global score?

Re: This comment is very prudent to elevate the quality of our MS. The following section has been added: “The Lysholm score for efficacy evaluation will be recorded at 12 months
postoperatively. The Lysholm score [20] ranges from 0–100 points and consists of 8 dimensions: a score of 80–100 points indicates elimination of all or the main symptoms, basic recovery of joint function, being capable of participating in normal labor and work (excellent); 60–79 points indicates elimination of all or the main symptoms, basic recovery or great improvement in the main function of the joint (good); and 0–59 points indicates no symptom improvement or symptom deterioration (poor). Efficiency = the number of excellent and good cases/the total number of cases × 100%.”

Statistical Analysis: in general the paragraph is too poor to be accepted.

Which dataset will you analyze? Intention to treat? Per-Protocol? Specify: results in protocols like yours could be very different.

Re: This comment is very prudent to elevate the quality of our MS. It has been revised to be “The analysis will be performed on the basis of the intent-to-treat principle. A full analysis set following the principle of intent-to-treat will consist of a data set for all patients who participated in the trial, regardless of compliance or withdrawal. For patients who are lost to follow-up, the missing data will be imputed by the last observation carried forward method based on the final observed value.”

No sample-size calculation is reported: what's the expected power of the results you will obtain?

Re: This comment is very prudent to elevate the quality of our MS. The statement of “sample size calculation” has been added as follows: “Based on our previous experience [23] and pilot study results, we assumed that the therapeutic efficiency on full-thickness cartilage injury of the knee joint would be 78% for microfracture surgery and 97% for autologous cell-derived tissue-engineered cartilage transplantation. Considering α = 0.05 (two-sided), and power = 80%, the necessary sample size was calculated as n = 84. With a predicted dropout rate of 20%, the required sample size was calculated as n = 50 per group.”

You only consider bivariate tests. chi-square, t-test, rank sum. I strongly suggest to use a multivariable approach and consider the introduction of surgeon effect as random component in the model.

For example, try read this paper [23] on the impact of surgeons in cardiac outcomes. It can be extended to your surgery protocols too.
Re: This comment is very prudent to elevate the quality of our MS. It has been revised to be “Descriptive statistics will be used for baseline feature data. Pearson chi-squared test or Fisher’s exact test will be used for intergroup comparisons of categorical variables, such as curative outcomes and postoperative incidence of adverse events. For independent variables, such as IKDC score, VAS score, T2 value and ΔR1, an independent sample t-test or Mann-Whitney U-test will be used.

A multivariate logistic regression analysis model will be used to adjust for possible confounding variables such as age, sex, etiology, cartilage defect area, meniscus injury, course of disease, severity of cartilage injury, postoperative complications, and surgeon (experience).”