Reviewer’s report

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

Version: 1 Date: 28 Sep 2017

Reviewer: Oscar Bortolami

Reviewer's report:

Please note that this report is for the original submission only and not the revised version.

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

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

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

Item 3: Date and version identifier: Not applicable

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

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

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

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
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

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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: compliant

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

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

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

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

Item 10: Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists). Eligibility criteria for surgeons missing

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

Item 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): compliant

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

Item 11d: Relevant concomitant care and interventions that are permitted or prohibited during the trial: missing

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.
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

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

Item 15: Strategies for achieving adequate participant enrolment to reach target sample size: missing

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).

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

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

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

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

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

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

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
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.

Item 20b: Methods for any additional analyses (eg, subgroup and adjusted analyses): not clear if such analyses will be performed

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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?

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.

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?

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?
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.

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

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 http://www.sciencedirect.com/science/article/pii/S1053077013004023 on the impact of surgeons in cardiac outcomes. It can be extended to your surgery protocols too.

Gianfranco Di Gennaro

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Please indicate the quality of language in the manuscript:

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