ISSCR

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

STEM CELL-BASED CLINICAL TRIALS:

PRACTICAL ADVICE FOR PHYSICIANS AND ETHICS / INSTITUTIONAL REVIEW BOARDS

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OVERVIEW

This guide is designed to help physicians and ethics/institutional review boards evaluate early-phase, stem cell-based clinical trials as they consider whether to run or approve such a trial. Fundamental questions, included within this guide, can be used to assess the cell product, the preclinical data, and the clinical trial, regardless of the disease or cell type used. Collectively, these questions serve as a resource to support the rigorous framework being developed to assess cell-based trials.

Stem cell therapies have the potential to repair or rebuild failing organs or networks of cells and in so doing, restore and prolong human health. The number of clinical trials using stem cell-derived approaches is increasing globally as translational research projects mature. In this emerging therapeutic area where national and international guidelines and standards are being developed, each stakeholder has a responsibility to rigorously assess these trials to ensure that they are well-designed and based on strong and rational preclinical evidence and that the potential therapy will be safe, effective, and meet patient needs. The risk of poorly designed or ineffective trials or, worse, testing unsafe interventions, could put patients at risk of serious harm and undermine the progress of the entire field.

While clinical trials are normally reviewed by national regulatory officials and/or local ethics/institutional review boards, the stakeholders also include physicians who have a vested professional interest in the implementation and outcome of the trial. The physicians running the trial want to help develop therapies for various conditions and are concerned about the health and safety of their patients. Collectively these three groups, each with a unique perspective, can and should provide 360-degree feedback of the trial, the need for which is particularly acute given the complexity of the products and therapeutic approaches. And while the regulatory authorities often have their own guidelines, this is typically not the case for clinicians or ethics/institutional review boards.

Recognizing that the primary stakeholders come from a variety of backgrounds, the International Society for Stem Cell Research (ISSCR) Committee on Clinical Translation, comprised of physicians active in this field, has developed a series of practical questions to access early phase, cell-based clinical trials, regardless of disease or approach. These fundamental questions are ones we would ask ourselves—and are important for physicians and all stakeholders assessing patient safety, professional risk, and potential for the success of a trial.

For a full list of questions, as well as signs of problematic trials, please see the accompanying tables. Additionally, a more detailed perspective on the development of this document can be found in the background section following the questions.

PRACTICAL QUESTIONS TO ASSESS A STEM CELL-BASED CLINICAL TRIAL

If any of the following questions cannot be satisfactorily answered based on the information provided by the sponsor or the literature, they should be resolved with the sponsor prior to approving or participating in the trial.

GENERAL QUESTIONS

- Has the trial been reviewed and approved[1] by an appropriate regulatory agency and/or undergone review by an ethics/institutional review board? If so, which agency?
- What is the stem cell-derived intervention being investigated? Is the therapeutic approach appropriate for the disease / injury in question and what is the rationale for using this cell product for the condition? What is its proposed mechanism of action? Does it make scientific and medical sense?
- Is the cellular intervention being tested likely to be competitive with other existing therapies /standard of care for this disease and thus worth investigating at this stage?

QUESTIONS RELATING TO THE CELL PRODUCT

- Is the source and derivation of the stem cells and differentiation of the progeny clearly defined?
- Has this stem cell product been derived and manufactured in accordance with appropriate guidelines and has the composition of the final product been clearly defined? By whom?
- Have the stem cells been genetically modified? If so, does this pose any safety risks?
- Is this a combination product such as cells plus some other agent (e.g. cytokines, scaffolding, or a device)? If so, has this other non-cellular agent been tested in humans? What were the results?
- Are the stem cells derived from allogeneic sources? Is immune rejection a possibility? If so, are immunosuppressive interventions required? What are their potential complications?

QUESTIONS RELATING TO THE PRECLINICAL DATA

- Do the cells display appropriate characteristics in culture and do they express the markers expected of such cells (e.g. action potentials with neurons, beating with cardiomyocytes, insulin production with beta-cells)? Or are they transplanted as progenitors and mature in the body. What is the evidence for this?
- Do the cells survive when transplanted into animal models of disease? If so, for how long and in what numbers? What is their biodistribution post-transplant - do they stay where they are injected or do they migrate to other sites? If so, where and in what numbers? Do they cause problems at these other sites?
- Have relevant toxicology studies been done with the cells? Have the cells been shown to be safe in animal models? Have they been tested for tumorigenicity?
- Do the transplanted cells ameliorate deficits in validated animal models of disease? What is the known or proposed mechanism of this therapeutic effect?
- Have the results been replicated in multiple, independent laboratories? Have attempts to repeat the results failed?
- Have the data from this work been published in reputable and appropriate, peer-reviewed publications and/or presented at international meetings? If so, where?
- Is the pre-clinical medium/long term safety data available for review?
- Has this specific cell product been previously tested in patients? If so, for what condition(s) and what were the results? What was the preliminary evidence for safety, efficacy, and toxicity?

[1]Note that this is not the same as a "registered" trial. Registration in a national database such as clinicaltrials.gov does not guarantee the trial is approved.

QUESTIONS RELATING TO THE TRIAL

Who designed the trial? Who is sponsoring the trial? Who is funding it? Why is the trial being funded in this way?
Do you know the company? Who is on the Scientific Advisory Board? Do they have appropriate expertise such as experience working on the disease of interest, the biology underlying it and/or the technology being used to treat it?
How will the cells be delivered? For example, intravenously or via a catheter or surgically? Has this delivery route been used before? Were there complications?
Why were you as the physician asked to be a PI in this trial?
Is the trial approved by an academic medical center ethics review / institutional review board (IRB) or a national equivalent? IRB/ethics approval is required for a trial.
Are there financial or other conflicts of interest associated with running this trial? Does the physician or patient / family stand to improperly benefit financially from the trial?
Is it clear what type of trial this is (e.g. first-in-human, safety study with dose escalation, etc)?
Are the patient selection criteria appropriate?
Are the trial endpoints well established for this disease? Are there clinical outcomes, or are surrogate endpoints such as biomarkers or imaging studies used?
If included, is the long-term follow-up sufficient - e.g. typically >1 year for most cell-based trials? Are the end points relevant to the treatment?
Are all the possible safety issues being looked at to your satisfaction?
What are the contingency plans for adverse reactions and complications?
Would you be willing to give this proposed intervention to your patients knowing the above? If not, what concerns to do you have? Have they been answered?

SIGNS OF A PROBLEMATIC STEM CELL-BASED CLINICAL TRIAL

The trial is not under the oversight of a regulatory body.

Trials should be subjected to rigorous regulatory and ethical/institutional review to ensure that the potential treatment conforms to the highest scientific and safety standards.

The science behind a disease does not match the science behind the treatment

Ensure that the scientific data adequately supports the approach and cell type being used.

The preclinical data supporting the efficacy and/or safety of the approach is lacking or unconvincing.

All preclinical data should be generated in a way that provides a precise, accurate and unbiased measure of clinical promise.

The trial requires the patient to pay to receive the experimental intervention.

"Pay-to-participate" trials pose challenges for ensuring the integrity of the trial. Typically, the cost of testing a new treatment and monitoring the trial is defrayed by the company developing it, a foundation, government funding, or a combination of these.

The qualifications of scientific and medical officers, the primary investigator and/or physician are not consistent with the science of the disease being investigated.

Collectively, the corporate leaders and physicians must be highly qualified to assess the outcomes of the treatment and manage potential complications, respectively.

BACKGROUND

INTRODUCTION

Stem cell science is progressing rapidly, and many currently untreatable diseases may be helped by cell-based therapies. Correspondingly the number of clinical trials using stem cell-derived approaches is increasing as translational research projects mature and reach the clinic. This clinical trials process is essential for rigorously assessing the efficacy and safety of potential treatments. However, not all experimental therapies that enter clinical trials are successful. There are many reasons for this, some of which could have been predicted based on the preclinical data and/or how the trial has been conducted (Perrin, S., 2014). The impact of a poorly designed intervention or, worse, a potentially unsafe therapy, runs the risk of undermining progress of the entire stem cell field as well as putting patients at risk of serious harm. It is therefore essential that any new clinical trial, especially one with a first-in-human stem cell-derived therapy, is thoroughly assessed prior to exposing patients to potentially ineffective or harmful therapies.

Who should ensure that a stem cell-derived clinical trial has been properly assessed? Each of the stake holders, the local and/or national regulatory agencies, local ethics/institutional review boards and the investigating physician(s), has an important and essential role to play in assessing a clinical trial. These groups, each with a unique perspective, must ensure that experimental therapies are founded on good scientific and medical evidence and that they meet the needs of the patient. This vigilance may become even more critical where there is less stringent oversight, where new technologies pose unique challenges and where expertise and standards are being developed.

Clinical trials of stem cell-derived cellular interventions have unique considerations that differ from pharmacological agents. However, not everyone involved with the assessments may be versed in assessing the merits of cell-based trials, especially clinicians and local research ethical/institutional review boards. This can lead to these critical individuals or committees relying heavily on the information being given to them by the sponsors of the trial. While this can be very informative, it is essential that those involved in running or reviewing the trial can independently assess the therapy and the information they have received and come to their own conclusions about the merits of taking it to patients.

To provide a resource for this process the ISSCR has developed a set of practical questions to assess a stem cell therapy. This document, developed by clinically active physicians, scientists and professionals who have had experience in this new therapeutic area, draws on principles and recommendations from the ISSCR's 2016 Guidelines for Stem Cell Research and Clinical Translation (ISSCR, 2016 and see associated commentary, Daley et al., 2016). The purpose of this guide is to help those involved in the process to better appreciate the details of what they are being asked to approve and give to their patients. It is not meant to be exhaustive nor used to police trials.

WHAT IS THIS GUIDE TRYING TO DO?

Clinical trials represent an important step in the development of emerging cellular therapies and are key to developing effective and credible treatments. As such, they are the antithesis of unregulated and potentially harmful "therapies" that are now too commonly being marketed across the globe (Turner and Knoepfler, 2016; Kuriyan et al., 2017). Assessing the quality of a trial can be difficult, especially in the nascent field of stem cell-derived interventions. While concerns of patient safety are paramount, strong consideration also should be given to the scientific basis for using the approach (London et al., 2010; Kimmelman and Federico, 2017) as well as its possible therapeutic benefits compared to current standard of care. While physician-investigators are provided with an Investigators Brochure, these lengthy documents can make the relevant data difficult to extract and may not address all questions.

This guide highlights essential questions, regardless of disease or approach, to consider prior to approving or running any early phase cell-based clinical trial. The questions focus on the preclinical data and the clinical trial while recognizing that there may be disease or treatment-specific questions beyond the scope of this resource. The purpose of the document is to provide individuals and/or committees with a set of independent questions so that they feel more confident they have covered the critical issues before approving or adopting the trial.

QUESTIONS RELATING TO THE STEM CELL PRODUCT AND PRECLINICAL DATA

It is important to understand what type of stem cell or derivative is being tested in the trial, its source, and its derivation. This not only ensures that the provenance of the cell is known, but that the risk that it might pose can be quantified (e.g. does it come from a stem cell source where the cells are highly proliferative; what manipulations have been made that might change its properties, is the cell immunogenic, etc). Furthermore, this also allows for an understanding of how that cell product is thought to work. Is it, for example, replacing cells lost in the disease process (e.g. islet cells with diabetes or cardiomyocytes with heart failure) or is it being used to deliver a host of released factors that are acting locally (e.g. mesenchymal stromal/stem cells)? One should carefully review trials involving cells whose mechanisms of action are undefined or merely given as "paracrine". Understanding the general rationale for the treatment approach being trialled is vital to assessing the pre-clinical work underpinning the clinical translation. For example, if cell replacement is the proposed mechanism, has it been shown in appropriate animal models that the cells survive long term in significant numbers and in a state that allows for them to exert functional benefits? Are those benefits comparable or better than those seen with agents that are already in clinical use? These are basic standards that any potential cellular therapy must demonstrate to be competitive in the clinical space.

Pre-clinical studies are essential for assessing safety, a primary concern of patients and regulatory authorities. Unlike drugs or biological agents, cells have the potential to persist for the patient's lifetime. It is important that preclinical studies document the biodistribution of the cells to assess whether seeding remote from the target organ occurs. Long-term studies should be done to assess tumorigenicity or local complications, e.g. arrhythmias in the heart, seizures or movement disorders in the CNS and so on. In addition to safety, there needs to be a scientifically-justifiable expectation of success based on the known biological characteristics of the cell. Namely, how robust are the pre-clinical efficacy data (Perrin, 2014)? Greater confidence can be had with translating a potential therapy to the clinic when the work that justifies its clinical adoption has been

published in peer reviewed journals and been demonstrated to work by independent groups. If reproducibility has been a problem with this approach, have the key variables responsible for this been defined? If many groups have studied these cells, is there general agreement as to efficacy, or is there still controversy in the field? While we recognize that the standard of independent reproducibility may not always be achievable for every new approach, when present, it increases the probability of clinical success.

QUESTIONS RELATING TO THE TRIAL ITSELF

The next stage of the assessment process is the trial itself. This can be difficult to assess, as often studies of this type have not been done before. Among the most important of these, are issues to do with how the trial has been reviewed and approved. Have the proper governmental and institutional and/or ethical reviews been conducted? Additionally, it is critically important to understand the trial design. Knowing who has been involved in the trial and its design can give one greater confidence if they are recognised as having the appropriate expertise in this therapeutic area and approach. This also applies to where the trial is being run (who is the PI for example), how it is funded, and who sits on the data monitoring and trial steering committees. Ask whether the PI has a financial stake in the trial, e.g. through ownership or consultancy with the corporate sponsors. While these issues should not solely dictate whether a trial takes place, they nevertheless provide confidence as to the expertise and experience that underlies its execution and thus the merit of the work.

Recognizing that trial designs will vary widely, it nonetheless is important to know whether this is a first-in-human study or later phase study. If this is phase 2 or beyond, what were the results from the earlier stages, both in terms of safety and efficacy? Are there contingency plans in place for potential adverse events? Are standard trial design elements like randomization, placebo controls, double-blinding, options for cross-over of placebo-treated patients, and appropriate statistical powering in place? How will the cells be administered? By intravenous injection? By catheter? By direct injection under image-guidance or surgical visualization? If delivery devices are used, have they been tested in humans previously and been approved by appropriate regulatory authorities?

Plans for long-term follow up, if included, should also be assessed. This is critical for assessing safety as well as signs of efficacy and therapeutic benefit (or complications) in any stem cell-based trial regardless of the phase. Transplanted cells may persist in the body indefinitely and thus effects may manifest well beyond the length of trial being supported. If long-term follow up is not built into the study from its inception, then questions must be asked as to why.

We hope that this short guide is useful to those who are faced with difficult decisions about taking stem cell-based approaches to clinic. It is not meant to be an absolute list of questions for considering whether such approaches do go to clinic, but rather an aid to help those who need and want more guidance in this area.

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