Stem Cell Trials for Cardiovascular Medicine: Ethical Rationale

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Stem cell-based interventions provide new treatment prospects for many disease conditions, including cardiovascular disorders. Clinical trials are necessary to collect adequate evidence on (long-term) safety and efficacy of novel interventions such as stem cells, but the design and launch of clinical trials, from first-in-human studies to larger randomized controlled trials (RCTs), is scientifically and ethically challenging. Stem cells are different from traditional pharmaceuticals, surgical procedures, and medical devices in the following ways: the novelty and complexity of stem cells, the invasiveness of the procedures, and the novel aim of regeneration. These specifics, combined with the characteristics of the study population, will have an impact on the design and ethics of RCTs. The recently closed JUVENTAS trial will serve as an example to identify the (interwoven) scientific and ethical challenges in the design and launch of stem cell RCTs. The JUVENTAS trial has investigated the efficacy of autologous bone marrow cells in end-stage vascular patients, in a double-blind sham-controlled design. We first describe the choices, considerations, and experiences of the JUVENTAS team. Subsequently, we identify the main ethical and scientific challenges and discuss what is important to consider in the design of future stem cell RCTs: assessment of risks and benefits, the choice for outcome measures, the choice for the comparator, the appropriate selection of participants, and adequate informed consent. Additionally, the stem cell field is highly in the spotlight due to the (commercial) interests and expectations. This warrants a cautious pace of translation and scrupulous set up of clinical trials, as failures could put the field in a negative light. At the same time, knowledge from clinical trials is necessary for the field to progress. We conclude that in the scientifically and ethically challenging field of stem cell RCTs, researchers and clinicians have to maneuver between the *Skylla* of hyper accelerated translation without rigorously conducted RCTs and the *Charybdis* of the missed opportunity of valuable knowledge.

Introduction

REGENERATIVE MEDICINE (RM) is an innovative, interdisciplinary field of complex interventions with the aim to restore the function of damaged or diseased tissue by stimulating *in vivo* repair.^{1,2} Due to aging and lifestyle factors, the prevalence of (chronic) degenerative diseases continues to increase.³ Stem- and progenitor cell-based interventions hold promise to meet the corollary growing demand for new regenerative therapies for the burden of chronic degenerative diseases, which includes orthopedic, cardiovascular, and neurological disorders.² Although early stem cell trials have been performed or are underway for many types of disorders, particularly using somatic stem cells like bone marrow (BM) cells and mesenchymal cells,^{4,5} translating novel experimental strategies to clinical therapies is time-consuming. In the meanwhile, stem cell clinics are taking advantage of

the hopes and expectations raised by stem cells and are already offering a wide variety of insufficiently proven stem cell treatments to patients in return for payment.^{6,7}

Conducting clinical trials, from first-in-human studies to larger randomized controlled trials (RCTs), is important to collect adequate evidence on (the long-term) safety and efficacy of novel interventions, but the design and launch of clinical trials is scientifically and ethically challenging, especially for stem cell interventions.^{8–10} Stem cells are different from traditional pharmaceuticals, surgical procedures, and medical devices in several ways. First, relatively little (pre)clinical knowledge is available from this rapidly growing, innovative field.^{8,9} Second, due to their complexity (e.g., due to variability and the dynamic character) and their potential long-term impact, stem cells are harder to investigate; moreover, animal models may not be good predictors of what happens in humans.^{8,11–14} Third, in contrast to traditional drug

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trials, insertion of stem cells requires an invasive procedure (ranging from injections to surgery). Fourth, the aim to regenerate tissues or organs, is also distinctive.^{8,15} In this study, we aim to investigate whether these features—combined with the characteristics of a specific study population—have an impact on the design and launch of clinical trials.

The majority of (pre)clinical research in the area of regenerative cardiovascular medicine focuses on cell interventions with different types of stem cells for acute myocardial infarction, chronic coronary artery disease, and peripheral artery disease (PAD). The recently completed JUVENTAS trial (NCT00371371) is the largest RCT studying cell-based interventions in the field of PAD to date.¹⁶ In this article, the JUVENTAS trial will serve as an example to identify the (interwoven) scientific and ethical challenges in the design and launch of stem cell RCTs. We first describe the choices that the JUVENTAS research team has made regarding these challenges, as well as the considerations and experiences during the trial. Subsequently, we retrospectively evaluate these aspects and discuss what is important to consider in the design of future stem cell RCTs.

The JUVENTAS Trial: Choices, Considerations, and Experiences

The rationale and design of the JUVENTAS (reJUVenating ENdothelial progenitor cells via Transcutaneous intra-Arterial Supplementation) study have been reported previously.¹⁶ The trial was registered in the clinicaltrials.gov website, and the results will be published in a peer-reviewed international journal according to CONSORT guidelines.¹⁷

In brief, the JUVENTAS trial is a phase II study, aimed at providing valid and reliable evidence on the efficacy and safety of intra-arterial injections of autologous BM-derived cells in patients with critical limb ischemia (CLI), the most advanced stage of PAD. The calculation of the sample size was between 110–160 participants.¹⁶

Efficacy was determined by the incidence of major amputations at 6 months, reflecting disease severity and progression. Besides this primary outcome, other clinical outcome measures were assessed, for example, the quality of life (QoL), for which generic instruments were used (EuroQoL 5-D, EQVAS, SF36). Surrogate outcome measures for perfusion, such as the arm-brachial index and transcutaneous oxygen measurements, were also incorporated.

A double-blind, sham-controlled design (allocation ratio 1:1) was chosen. Since the decision to amputate is both physician and patient driven, a sham intervention eliminates bias with respect to the decision and timing of amputation.¹⁸ Specific measures were taken to warrant blinding of both patient and investigator-physician. Autologous erythrocytes were added to the saline fluid to match the color with the BM cell product; in addition, to correct for the specific odor of dimethylsulfoxide (DMSO) used in the cell preparation, the same amount of DMSO was added to the placebo. All participants underwent BM aspiration and biopsy, under local anesthesia and conscious sedation. Thereafter, the patients were given repetitive intra-arterial injections of BM cells or saline (three times at 3-week intervals). BM cells of the control group were stored, and would be offered to the patients should the intervention show benefits to the cell intervention group on the condition that these participants would be

monitored and incorporated in a clinical study to gain additional knowledge. Based on information from interviews with JUVENTAS investigators (M.T. and M.V.), double blinding was adequately maintained during the trial.

The JUVENTAS trial included advanced stage PAD patients with no surgical or endovascular revascularization option. Patients with severe pain (intermittent or persistent) or tissue loss (demonstrated by ulcers) were eligible for inclusion. In these no-option patients, potential risks were considered acceptable given the poor prognosis and the lack of alternative treatments. Furthermore, previous evidence pointed toward efficacy in advanced stage PAD patients,¹⁹ whereas data on the efficacy of cell interventions in less advanced stages of PAD were not available.

The full study procedure was anticipated to impose a burden on study participants due to frequent hospital visits and the expected pain and discomfort caused by the procedures. The physical risks related to BM aspirations and intra-arterial injections were transient and would thus not lead to increased risk of death or permanent disability. Previous clinical studies on BM cell administration in patients with limb or myocardial ischemia had not shown major short-term side effects.^{19,20} Renal and liver function measurements were performed at inclusion as well as before and after each intra-arterial infusion. All-cause mortality, occurrence of malignancy, or hospitalization due to infection were recorded. During the trial, all (serious) adverse events were recorded and processed according to national guidelines. An independent Data and Safety Monitoring Board (DSMB) evaluated the safety and efficacy through sequential monitoring. The stopping rule regarding efficacy would be fulfilled if the observed benefit in the cell intervention group was clearly larger or if the sham group appeared to be better than BM cell infusion, based on the assumption of a 50% reduction of major amputations. The stopping rule of safety would be applicable if mortality of 34% or more in the intervention group occurred, based on an expected mortality of 23% within 6 months.

The prevalent concomitant cardiovascular risk factors among the participants were expected to negatively influence the quality and amount of BM progenitor cells, and consequently the outcome of the intervention.^{21–23} Therefore, a secondary aim of the study was to characterize BM progenitor cell dysfunction in patients with PAD and relate BM progenitor cell function with a clinical outcome.²¹

Patients were recruited through their vascular surgeon. After receiving a patient information form, the potential participant had an appointment with the coordinating investigator-physician. Patients received a patient information letter and a DVD that presented a random JUVENTAS patient who had already undergone the procedure. Patients were given 1 to 2 weeks to consider their decision.

The investigators had the impression that most participants understood the information during the first appointment. Random checking of participants' understanding during the course of the trial showed that many patients still remembered the information provided at inclusion; however, some patients were not fully aware of the fact that they could also receive a sham procedure, either because they had forgotten or had misunderstood the information. Investigators increased the assessment of participants' knowledge both at inclusion and during the trial. The effects of these measures were not systematically evaluated.

Inclusion of patients in the trial was slower than anticipated due to the fact that fewer no-option CLI patients than expected were referred for the trial and because a substantial proportion ($n=100$) of referred patients chose not to participate after detailed discussion of trial information. The latter could result from the relative uncertainty with respect to the effect of the stem cell intervention, the inconvenience related to participation, and the 50% chance to be randomized to the sham intervention arm.

Discussion

The design and setup of clinical trials involves many normative relevant decisions. It has been shown previously that certain issues are key when translating RM interventions into clinical studies.^{8,9,11,13} These issues will be discussed below in relation to stem cell RCTs, with the JUVENTAS trial as an example.

Risks to participants and potential benefits to science, society and participants

The principle that risks to participants must be proportional to the anticipated benefits is common to all international documents on clinical research ethics.²⁴ The earlier the phase of a clinical trial, the more likely the benefits accrue to science and society instead of the participant—while the participants in all phases are exposed to burdens and risks.²⁵ Before it is possible to evaluate the proportionality of risks to benefits, both risks and benefits should be analyzed. Investigating innovative interventions inherently involves uncertainty about risks and benefits, although the extent of uncertainty depends on the type of (stem) cells, previous evidence, and experience with so-called reference classes, that is, agents with similar mechanism of action.^{10,26} In general, this uncertainty is higher in RM than in traditional pharmaceuticals, due to the variability of the product—particularly for autologous cell products, the complex mechanism of action, and the dissimilarity between animal models and humans.^{10,14} In the JUVENTAS trial, the variability of the number of cells was documented and related to study outcome.

However, in a phase II trial, such as the JUVENTAS study, short-term safety of the cell injections had already been demonstrated by phase I studies, including studies investigating autologous cells for other types, but similar indications (reference classes), such as in cardiology.^{19,20} Besides the risks and uncertainty related to the cells, there are inherent risks to the invasive procedures. In the JUVENTAS trial, these were the BM aspiration and the intra-arterial injections, of which the risks are moderate and well-known as these are standardized procedures. The psychological burdens were relatively high due to the inconvenience to undergo multiple invasive procedures, the uncertainty in which arm the participant was randomized, and the possibility of receiving a sham intervention.^{27,28}

Previous trial data had shown that individual benefits might occur, although studies were small and often uncontrolled.¹⁹ Besides potential individual benefits, a clinical study should also benefit science and society, that is, have social value. In the JUVENTAS trial, social value was expected to be high due to various reasons. First of all, the randomization to a sham group increased the scientific validity of the study, and

thus the potential benefit to science and clinical practice (see also paragraph “need and acceptability of sham procedures”). Second, the choice of the number of major amputations as a primary outcome measure was a clinically relevant outcome, which had been used previously in other trials, and therefore enhanced the comparability with previous studies and improve interpretation. Third, knowledge value was enhanced since preclinical studies into the characterization of BM progenitor cells were stimulated and related to clinical outcome. This is also called reciprocal value, which is mainly aimed at gaining insight into the working mechanism. This also ensures that if no beneficial results are shown the trial still stimulates further research.²⁹ Stimulating reciprocal value is important in a young and innovative field as much is still unknown about working mechanisms (see also next paragraph).

To acquire a favorable risk–benefit ratio, careful efforts should be made to minimize risks and enhance individual benefits and benefits to science and society. Monitoring by a DSMB is essential to review serious adverse events and to make recommendations about continuation or modification of the trial.³⁰ To enhance benefits to science and society, negative results should be published.^{13,30} Furthermore, these benefits can be enhanced by trial registration, collection of standard data elements, and publication of the protocol through the guideline of CONSORT.¹⁷

In conclusion, the risks to participants in the JUVENTAS trial could be justified both by the benefits to science and society and by potential clinical benefits for the intervention group.³¹

Outcome measures: demonstrating clinical improvement and/or working mechanism

Within the field of RM, discussion exists whether the endpoint in clinical trials should be regeneration or clinical improvement.⁸ By choosing amputation as a primary outcome, the JUVENTAS trial focused on clinical improvement. An outcome measure assessing regeneration, that is, neovascularization could have provided important mechanistic insight; however, providing results on neovascularization by itself would offer little information on clinical outcome. Next to this, at this moment, no widely used reliable and direct test of neovascularization or blood flow at the tissue level in ischemic limbs is available.³² An imperfect measure would have led to burden, risks, and costs without benefits and was therefore not included. Although testing amputated tissues would provide information on neovascularization, this would only be possible in a subpopulation of patients that likely has responded poorly to the intervention, and would not provide relevant information. Furthermore, no reliable methods are available to track the injected BM cells in humans.

However, the JUVENTAS trial did collect indirect information about the working mechanism of the BM cells and indirectly about the regenerative capacity. The secondary outcome measures (e.g., ankle–brachial index and transcutaneous oxygen measurements) are surrogate measures that are widely used and available in daily clinical practice and indirectly reflect perfusion alterations. As mentioned in the previous paragraph, the JUVENTAS team also ensured that future research will be performed to investigate whether particular cellular characteristics are related to clinical outcome.

Clinical improvement in CLI can be assessed by various outcome measures. The amputation rate or amputation-free survival (AFS), a composite metric combining the outcomes of mortality and amputation, have been proposed as preferred measures in CLI.³³ However, the outcome measure of amputation or AFS might not fully capture the patient's perspective.³⁴ Limb salvage with no further improvement in pain-free walking or QoL is not necessarily a favorable result for the patient. Health-related QoL may be considered as a primary outcome measure, for which valid questionnaires are available.³⁵ Whereas amputation appears to be a harder endpoint than QoL (as it is easy to quantify), the decision of amputation is patient and physician driven, and thus influenced by subjective factors as well. Therefore, in a stem cell RCT with clinical improvements as an outcome measure, blinding of both participants and physicians is essential to manage bias. Apart from which outcome measures are chosen, it is useful that outcome measures are uniformly used in future trials to facilitate the comparison of the results, and thus, to stimulate benefits to science and society.

Need and acceptability of sham procedures

In RCTs, a double-blind design is considered to provide the highest level of evidence, if it is expected that the outcome measures are influenced by placebo effects. Other reasons to blind participants and/or investigators are to distinguish specific intervention effects from nonspecific effects such as reporting bias, performance bias, and to prevent different withdrawal from the two arms.^{36,37} One of the ways to blind both the investigator and the patient is to use a placebo. The use of placebo in itself is ethically challenging, but even more so when it involves invasive procedures with inherent risks, which is the case for so-called sham interventions.^{38,39} As stem cell interventions often require invasive procedures, determining whether there is a methodological necessity and acceptability of sham interventions is important. As the primary endpoint in the JUVENTAS trial contained subjective elements, a sham is methodologically necessary. Further, in the stem cell field, placebo effects and reporting bias of the participant and investigator-physician are expected to be enhanced due to (1) the invasiveness,⁴⁰⁻⁴³ and (2) high appeal of the stem cell field, which might increase expectations.

However, if the physical (and psychological) risks of sham procedures are disproportionate to the social value, or an alternative treatment that provides net medical advantage is available, the use of sham is unacceptable.⁴⁴ For the participants, in the JUVENTAS trial, there was no effective alternative treatment, and thus, a control group with sham was considered ethically acceptable. The sham in this trial contained multiple invasive procedures with moderate risks and burden. A possibility to lower the risks related to the incorporation of a sham could have been to perform a BM aspiration in the comparator group without true aspiration of BM. Whereas the investigator performing the procedure is not blinded anymore, the investigator conducting the procedure could be different from the person conducting the other study procedures to maintain blinding for the rest of the team. However, the more persons are aware of the type of allocated procedure, the more difficult it becomes to maintain blinding.⁴⁵ Thus, the JUVENTAS team made the choice to perform the full sham procedure to ensure blinding.

Challenges in choosing appropriate participants

Choosing an appropriate study population is another important ethical requirement in clinical research.²⁴ Several models of participant selection exist: the "healthy volunteer model," the "stable patient model," and the "oncology model" of treatment refractory patients.^{8,46} It depends, among others, on the aim of the study, and the toxicity of the intervention as to which population is most appropriate.^{47,48}

End-stage PAD patients were included since previous clinical studies had mainly demonstrated safety and a possibility of efficacy in this participant group.¹⁹ Another justification for choosing end-stage patients is that these patients have less quality adjusted life years (QALY) to lose, especially when it concerns seriously ill patients with CLI who are not eligible for conventional therapies.^{47,49} On the other hand, one could speculate that patients with less advanced stage may have a higher regenerative potential, and potential benefits as there is a less affected arterial system and possibly less dysfunction of the BM cell compartment.

Challenges in adequate information and consent

An adequate informed consent procedure is required to respect and protect the autonomy of participants.²⁴ Informed consent contains five essential aspects: competence, disclosure, understanding, voluntariness, and consent.⁵⁰ Competence might be impaired in advanced stage participants due to diminished cognitive capacity related to cardiovascular comorbidities and age. In general, disclosure of information to participants on the benefits and risks is relatively difficult as uncertainty is high in innovative fields. However, in a phase II trial, participants can be informed about the short-term safety and the potential for benefits of the cell interventions due to phase I trials. Furthermore, if standardized procedures are used, the risks of these interventions are well-known, such as the BM aspiration and intra-arterial infusions in the JUVENTAS trial. Furthermore, challenges with respect to understanding the provided information by the participants can occur, due to the chance of therapeutic misconception (TM) and therapeutic misestimation.⁵¹ In the JUVENTAS trial, the participants appeared prone to TM, that is, misunderstanding that the study has a scientific aim instead of clinical care.^{52,53} TM could be a sign that the participant does not understand the implications of the decision to participate in a trial, and validity of consent is then problematic. TM is difficult to assess as this can manifest inconsistently in the same person.⁵³ Three factors may contribute to the occurrence of TM in the JUVENTAS trial: the characteristics of the study population, the appealing character of stem cell interventions, and the invasiveness of the procedures. Participants with advanced or end-stage disease "continue to see themselves as patients seeking treatments," and are therefore at higher risk of TM.^{53,54} In addition, participants with a low education grade and a high age are also more prone to TM, as is applicable to the JUVENTAS trial participants.^{55,56} In a high-profile field like stem cell research, the expectations of researchers and participants are high and could fuel TM.^{57,58} Further, it has been speculated that the use of an invasive intervention in participants could foster TM.⁵⁹ In studies, in which the sham group might receive the cell intervention if proven effective after analysis of the study results, as in the JUVENTAS trial, one should also be extra

aware of TM. Hardly any sign of TM was identified at the start of the JUVENTAS trial. However, during the trial, it emerged that some participants were not aware of the chance of sham procedures suggesting that some participants thought they underwent a therapeutic procedure. Linguistic aspects in the oral or written information could encourage TM, if words like cell therapy or cell treatment are used.^{57,60}

Independent or coexistent with TM, hopeful participants are more likely to underestimate risks and overestimate benefits, which has been called therapeutic misestimation.^{51,54} It is important to distinguish the existence of TM and therapeutic misestimation from therapeutic optimism. Therapeutic optimism means that the participants hope that individual benefits exist, which does not necessarily imply an inadequate understanding.⁵¹ Efforts should be made to enhance the participant's understanding, both through the content as well as the manner of providing the information, through different manners, such as repeating information, face-to-face communication, audiovisual information, and offering to consult an independent party participants' comprehension, could be enhanced.^{53,61} With regard to the content of information, the difference between research and clinical care should be stressed, and probability data of risks and benefits in several forms should be given, as far as

possible.⁵¹ Confusing linguistics need to be avoided.^{53,54,60} In studies where the control group may receive the intervention after completion of the trial, it is especially important to stress the uncertainty of this. In participant groups similar to the JUVENTAS trial, the patients should be informed that the chance for the control group to receive stem cells (if proven effective) is relatively low due to high mortality (and amputation) rates among the participants. It is recommended to systematically check the understanding of information during a trial, especially of possibly receiving a sham intervention to prevent TM.

Conclusion

Whereas the design and setting up of RCTs inherently involves normative considerations, our evaluation of the JUVENTAS trial shows that stem cell RCTs raise specific ethical challenges due to the specific characteristics of stem cells. Although we evaluated only one particular study, the considerations are largely applicable to stem cell RCTs that use other types of stem cells and other fields than cardiovascular medicine (Table 1).

First, assessing risks and benefits is more challenging as the novel character and complex nature of stem cells cause

TABLE 1. ETHICAL CHALLENGES AND CONSIDERATIONS IN STEM CELL RANDOMIZED CONTROLLED TRIALS FOR CARDIOVASCULAR MEDICINE

<i>Ethical challenge</i>	<i>Points to consider</i>
Risk-benefit assessment	<p>Be aware of the uncertainty of risks and benefits; this depends on type of stem cells, previous evidence and experience with reference classes</p> <p>Be aware that there are physical risks due to invasiveness of the intervention, and psychological burdens due to randomization</p> <p>Make sure to manage and, if possible, minimize risks</p> <p>Be aware that the earlier the phase of a clinical trial the more likely the benefits of a trial accrue to science and society instead of the participant, while risks and uncertainty fall to the individual participant in all phases</p> <p>Make sure to maximize benefits, including knowledge value about working mechanism</p>
Choice for outcome measures	<p>Be aware that clinical improvement as outcome measure is important, but consider whether this fully captures patient's perspective</p> <p>Be aware that clinical improvement is affected by placebo effects and other nonspecific effects and consider to elude this by blinding</p> <p>Consider to incorporate outcome measures that assesses (directly or indirectly) regeneration to increase information about working mechanism (if a reliable test is available)</p> <p>Be aware that regeneration might not correlate with clinical outcome</p>
Choice for comparator	<p>Consider whether there is a treatment in clinical practice that provides net medical advantage, which should not be withheld to the comparator group</p> <p>Consider whether sham is methodologically necessary, among others, depending on type of outcome measure, and chance of placebo effects</p> <p>If sham is desirable, consider whether physical and psychological risks are proportionate to expected benefits to science and society</p>
Participant selection	<p>Consider which participant group is most appropriate. This depends, among others, on the aim of the study, and the toxicity of the intervention</p> <p>Be aware that in end-stage participants:</p> <ul style="list-style-type: none"> • Occurrence of harms may be more acceptable • Demonstrating efficacy could be impaired because of highly degenerative state (and autologous cells could be less functional)
Adequate informed consent	<p>Be aware that the risk of therapeutic misconception may be increased due to use of invasive intervention, and high expectations</p> <p>Be aware that the chance of therapeutic misconception is higher if sham as comparator is used, and if no option participants are included</p> <p>Next to therapeutic misconception, be also aware of therapeutic misestimation of benefits and risks</p> <p>Enhance informed consent procedure, both through the manner and content of information</p>

more uncertainty in comparison to traditional pharmaceuticals. This uncertainty depends on the type of stem cells, the phase of the trial, and the experience with reference classes. Besides the risks and uncertainty related to the cells, other aspects such as the invasiveness of the intervention, randomization, and the inclusion of a sham procedure cause physical risks or psychological burden in stem cell RCTs. Especially in a relatively young developing field, it is important to enhance the value of a study by collecting information about working mechanism, for example, by using regeneration (or surrogate outcome measures) as endpoint (if possible), besides clinical outcomes.

Second, while the direct aim of stem cell-based interventions is to regenerate, an outcome measure that reflects clinical improvement is considered to be more relevant for future patients. Outcome measures should be uniformly used in future trials to facilitate comparison of results. It is important that reliable endpoints are developed to assess regeneration and tracking of cells, to increase insight in the working mechanism of stem cells.

Third, due to the invasiveness of stem cell-based interventions and increased likelihood of placebo effects, sham procedures are considered methodologically necessary. However, sham procedures are only ethically acceptable when physical and psychological risks are proportionate to the scientific and societal benefits of including a sham, and when other conditions such as gaining valid informed consent are fulfilled. A problem related to the incorporation of sham is that it makes participation less attractive.

Fourth, the choice of participants codetermines the risk-benefit ratio. Whereas the occurrence of harms in an RCT may have the least impact in advanced stage participants, the likelihood of benefits may be small in this group.

Fifth, obtaining informed consent is more challenging since this type of participant is more likely to misunderstand the purpose, risks, and potential benefits of the trial. The risk of TM could be further increased by the use of invasive interventions, and by the novelty and promise of regeneration, which creates high appeal and high expectations. Hence, a moral obligation exists to ensure adequate disclosure and understanding of information by the participants.

Sixth, another difference with other intervention trials that has not been explicitly discussed here so far is the tense climate in which stem cell trials take place. A climate of high (commercial) interests among companies, researchers, and desperate patients, and the worldwide presence of stem cell clinics put pressure on the field. The high interests stimulate hyper accelerated translation of interventions into the clinic.^{62–65} Small companies are often involved in the development of RM interventions that need a quick return on investment and are not capable of financing large, long lasting, expensive clinical trials.^{63,66} This motive counts especially for off-the shelf available (allogeneic) RM interventions that are commercially interesting.^{67,68} The high public and commercial excitement also cause stem cell clinics to gain more terrain, which can put patients at unnecessary risks and costs, and hinder the progress of clinical trials.^{7,69,70}

The stem cell field is in the spotlight. This warrants a cautious pace of translation and scrupulous set up of clinical trials, as failures could put the field in a negative light, as occurred in the field of gene transfer.⁶⁵ At the same time, knowledge from clinical trials is necessary for the field to

progress. Further, it could prevent that nonevidence-based invasive stem cell treatments find their way into commercial clinics, which may pose unacceptable risks to patients. Therefore, researchers and clinicians in the stem cell field have to maneuver between the *Skylla* of hyper accelerated translation without scrupulously conducted RCTs and the *Charybdis* of the missed opportunity of valuable knowledge.

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Disclosure Statement

S.N., H.H., J.v.D., and A.B. do not have any financial or other competing interests to declare.

M.T. and M.V. were primary investigators in the JUVENTAS trial.

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