Participant selection for preventive Regenerative Medicine trials: ethical challenges of selecting individuals at risk

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ABSTRACT

The innovative field of Regenerative Medicine (RM) is expected to extend the possibilities of prevention or early treatment in healthcare. Increasingly, clinical trials will be developed for people at risk of disease to investigate these RM interventions. These individuals at risk are characterised by their susceptibility for developing clinically manifest disease in future due to the existence of degenerative abnormalities. So far, there has been little debate about the ethical appropriateness of including such individuals at risk in clinical trials. We discuss three main challenges of selecting this participant model for testing RM interventions: the challenge of achieving a proportional risk–benefit balance; complexities in the trial design in terms of follow-up and sample size; and the difficulty of obtaining informed consent due to the many uncertainties. We conclude that selecting the model is not ethically justifiable for first-in-man trials with RM interventions due to the high risks and uncertainties. However, the model can be ethically appropriate for testing the efficacy of RM interventions under the following conditions: interventions should be low risk; the degenerative abnormalities (and other risk factors) should be strongly related with disease within a short time frame; robust preclinical evidence of efficacy needs to be present; and the informed consent procedure should contain extra safeguards with regard to communication on uncertainties.

INTRODUCTION

Rather than managing symptoms of disease, Regenerative Medicine (RM) aims to restore the function of damaged or diseased tissue. Using a wide range of different techniques—including stem cell transplantation, tissue engineering and gene transfer—the body's natural ability to heal itself can be boosted, and damaged tissue can be replaced or regenerated. Cures are sought not only for many medical conditions, such as osteoarthritis and macular degeneration, but also for physical damage to tissue. Hopes are high that the progression of, for instance, degenerative neurological conditions, such as Parkinson's disease and amyotrophic lateral sclerosis degeneration, can be reduced by stem cell-based transplantation. Some of these techniques are regarded most effective in curing disease by preventing degeneration, and thus need to be applied early in a disease process.[1 2] In order to examine the effectiveness of these preventive RM interventions, it is necessary to test them in individuals the intervention is aimed at: *individuals at risk*. These individuals are characterised by their possible susceptibility for developing clinically manifest disease in future, but they suffer neither from symptoms nor from disease at trial inclusion (figure 1). For example, patients undergoing a partial medial meniscectomy (the partial removal of the medial meniscus) have a 10- to 20-fold increased risk of knee osteoarthritis later in life. In a clinical trial, patients undergoing this procedure were given an intra-articular injection of mesenchymal stem cells to test the (safety and) potential preventative effects of mesenchymal stem cells on osteoarthritic changes of the knee.[3] At trial inclusion, the participants did not suffer from osteoarthritis of the knee; non-symptomatic individuals were thus exposed to risks.

The individual at risk-participant model itself is not new: individuals at risk of, for example, cardiovascular disease or diabetes have participated in low-risk trials examining the effect of preventive medication or lifestyle measures for decades.[4] However, there has been little debate about the ethics of selecting individuals at risk for research.[2] Indeed, the debate on participant selection has centred around three other participant models (ie, participant populations in clinical research): the *healthy volunteer* model, the *stable patient* model, and the *advanced stage patient* model (figure 1).[5–7] *Healthy volunteers* are often considered suitable to include in phase I trials because they deliver reliable knowledge on safety, pharmacodynamics and pharmacokinetics, due to a lack of comorbidities or cointerventions. For potentially more risky phase I trials, as well as phase II and III trials, either stable (medically controlled) or advanced stage (no treatment options left) patients are considered more appropriate.[5 6]

In this paper, we examine the ethical acceptability of selecting the *individual at risk* model for clinical trials examining preventative RM interventions. We acknowledge that public discussion is needed on the desirability of these preventative RM interventions. Indeed, healthcare resources are finite, and justice issues arise when these high-cost preventive technologies are developed.[8] Moreover, these high tech, medical interventions may increase the medicalisation of our society as well as possibly decreasing the well-being of individuals because of a focus on future health problems.[9] However, as trials enrolling individuals at risk are taking place, initiation of the ethical discussion on this participant model in high-risk trials is necessary. Here, we focus on three main challenges that arise when selecting the individual at risk model for *testing* RM interventions.

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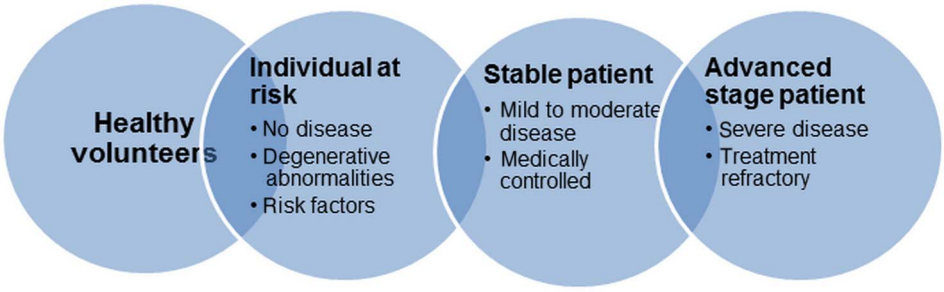

Figure 1 The four-participant model, according to their stage in disease development.

THE CHALLENGE OF REACHING RISK–BENEFIT PROPORTIONALITY

The principle that risks to research participants must be proportional to anticipated benefits is common to all international documents on ethical conduct in clinical research. This balance is difficult to ascertain for phase I studies because they are designed to determine the risks; and participants are not expected to gain any direct benefit (particularly because of the dose-escalation regimen).[10] Phase I RM trials carry additional concerns[8 11–15]: first of all, there are risks of standardised invasive surgical procedures used to administer RM technology, such as the risks of infections or haemorrhage.[16] Second, often the RM interventions themselves are accompanied by uncertainties, for example, the risk of developing cancers in pluripotent stem cell-derived interventions, or the risks of immunological complications due to the use of vectors in gene transfer. Moreover, many of the RM interventions are irreversible, and variable, because of their often personalised nature.[17] Besides these uncertainties, there may be risks we have no prior knowledge of (ignorance) because of an absence of interventions similar in mode of action, and the limitations of animal models.[13]

As individuals at risk have relative higher opportunity costs (they have more quality adjusted years of life to forego), one can question whether it is justified to expose them to the increased risks of phase I RM trials. Moreover, there may be additional dangers for individuals at risk. It is possible that participation in a trial is perceived as protection from disease. This could lead to a discontinuation of (other) effective preventive measures, which, in turn, increases their physical risks;[18] although, similar to healthy volunteers, they may be better at tolerating physical risks due to their healthier status.[5] Besides these *physical risks*, there are some *psychological risks*.[19] We speculate that these at-risk participants may start losing confidence in their health, as they become aware of potentially developing a disease in future. Enrolling patients undergoing a meniscectomy in a preventative osteoarthritis trial is drawing their attention to the fact that they are potential future patients with osteoarthritis. As a consequence, individuals may feel pressured to undergo the potentially preventive intervention, as they can otherwise be blamed for getting diseased later in life.[9] These psychological risks are not restricted to participants in clinical trials, but are applicable to RM interventions aimed at individuals at risk in general.

THE COMPLEX DESIGN OF EFFICACY TRIALS FOR PREVENTION

A second challenge is the complexity of the design of preventive phase II and III trials. To demonstrate the effect of the RM technology on prevention, a long follow-up is necessary because disease still needs developing. Patients whose medial meniscus is (partially) removed may not develop radiographic evident osteoarthritis until many years later. Therefore, trials examining the effect of mesenchymal stem cells on osteoarthritis would take years. Moreover, to obtain statistically reliable and valid results, a large sample size is required because participants will probably, but not necessarily, manifest clinical disease. Both a long follow-up and a large sample size may be difficult to achieve; the former because participants might withdraw or are lost to follow-up, and the latter because it may simply be too difficult to recruit many individuals, among others since these individuals are not symptomatic yet.

DISCLOSURE AND UNDERSTANDING IN INFORMED CONSENT PROCEDURE IS COMPLICATED

The third challenge is obtaining adequate informed consent from individuals at risk, as it may be difficult for participants to *understand* the information on innovative trials due to the many uncertainties, especially when explained in terms of percentages.[20 21] Moreover, it is genuinely uncertain if, when and how individuals at risk will manifest clinical disease. Last, dilemma arises to what extent, besides risks, uncertainties should be disclosed.[11 21]

ETHICAL ACCEPTABILITY OF THE INDIVIDUAL AT RISK MODEL IN RM TRIALS

Because of the relatively high risks and uncertainties of preventative RM, and the relative high opportunity costs of individuals at risk, we argue that this participant model is not appropriate for phase I trials. If preclinical studies show that RM interventions are expected to be most effective when applied in an early stage, and individuals at risk are the target population for the intervention, it is unavoidable to enrol individuals at risk to demonstrate efficacy in later phase trials. Since uncertainties decline during translation, the selection of the individual at risk model could be acceptable in following phases of research under certain conditions: when the intervention is low risk ánd the risks are proportional to the benefits; the follow-up time is short; the sample size is low; and the informed consent procedure is valid. In addition, one should assure that preclinical evidence is strong by adequate randomisation and blinding.[22] Researchers should make efforts to minimise the risks and enhance the benefits in order to increase the risk–benefit proportionality. To increase the anticipated social value of the trial, it is especially important that trials target diseases with a strong and timely relation between degenerative abnormalities (and other risk factors) and clinically manifest disease. In addition, this allows for a reduction in follow-up time and sample size which, in turn, minimises the overall risks and burdens to participants and also reduces the complexity of the trial design. If possible, one should consider using surrogate outcome measures that are highly related with clinical outcomes

as these often require a shorter duration of trials.[23] In order to prevent misunderstanding in the informed consent procedure, one should pay attention to an adequate manner of risk and uncertainty communication, for example, by presenting these visually such as in graphics.[24]

CONCLUDING REMARKS

We expect an increase in the use of the individual at risk model due to the development of (preventative) RM. Three main challenges arise when including this model in a RM trial: achieving risk–benefit proportionality; designing an efficacy trial in terms of follow-up and sample size; and obtaining valid informed consent. We conclude that selecting this model is not ethically justified for phase I RM interventions; however, under strict conditions, this model could be appropriate for phase II and III (efficacy) trials. We believe that early initiation of the ethical debate on the challenges for selecting these individuals for research allows responsible innovation of new preventive technologies.

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Contributors All authors were involved in the design of the manuscript. SLN and MGJLH wrote the drafts and final manuscript. ALB, JJMvD and WJAD commented on the drafts and approved the final version of the manuscript. All authors read and approved the final manuscript.

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