The ethics of bringing Regenerative Medicine to patients: the example of orthopedics

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De ethische uitdagingen van de translatie van Regeneratieve Geneeskunde naar de patiënt: de orthopedie als voorbeeld

(met een samenvatting in het Nederlands)

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Voor Stephan, pap en mam

CONTENTS

Chapter 1.

General introduction

This thesis identifies and evaluates the ethical challenges in the translation of Regenerative Medicine (RM) into clinical trials and society, mainly using orthopedics as an exemplary case. RM is a set of cutting-edge technologies in the medical field. The translation from preclinical studies to clinical studies and application in clinical practice and society is increasingly considered: a move from bench to bedside is expected. In order to guarantee sustainable, morally sound innovation, it is now time to systematically analyze the ethical challenges involved. Well-known ethical principles of clinical research, such as informed consent, fair participant selection, a proportional risk-benefit ratio, and scientific validity, should be evaluated in the context of RM. Furthermore, in an early phase of technology development the potential implications for society need to be taken into account when steering is still possible.

The aim of Regenerative Medicine

The word 'Regenerative' reveals the aim of this field of technologies: regeneration originated from the Latin word verb 'regenerare' which means 'create again'. Parts of the human body can regenerate spontaneously, once damaged. This was already known in ancient times, as appears from the Greek myth of Prometheus: Zeus punished the Titan Prometheus for stealing the fire of the Olympic gods. He was bound to a rock where an eagle ate his liver during daytime, which regrew during night. Hence, the Titan was exposed to perpetual torture, if Hercules had not freed him, 30.000 years later (1).
RM is not defined by a particular technology. Instead, it is an umbrella term for the research and clinical applications that share a scientific aspiration: to restore the original function of damaged or diseased tissue by stimulating the body's own repair (2). RM is said to be a new paradigm within medicine due to the goal of deliberately inducing regeneration (3). Next to that, RM is also characterized by its interdisciplinary nature. Among others, material sciences, informatics, stem cell biology, genetics, developmental biology, and surgery work together to understand the complex processes of growth and development in our body, with the ultimate aim of developing therapeutic techniques (2).
In addition to the liver, muscles, bone and epidermis can regenerate to a certain extent, but in many tissues the capacity to form novel tissue is limited: otherwise, we would live eternally (4). Due to all types of causes, such as congenital defects, acquired diseases, traumatic injuries, and ageing, our tissues and organs lose their function. To give three examples: the cartilage of our knees, which functions as a shock absorber, gradually wears during our lifetime, causing pain and mobility problems, also called osteoarthritis. After a heart attack, heart muscle cells are lost leading to a reduced pump function, and eventually chronic heart failure. Due to a car accident a person can become paraplegic due to a complete thoracic spinal cord injury as the neurons are damaged. Although painkillers, antihypertensive medication, and physiotherapy can reduce symptoms, these do not restore the tissue itself. Also a surgical

procedure can be effective, but the original function of the tissue is not retrieved and surgery often involves high risks and requires hospitalization. For example, in orthopedics the prosthesis is a very successful end-stage treatment for severe osteoarthritis, but never has the same properties as a real knee. Furthermore, in relatively young patients these are not preferred due to the prosthesis' limited life-span. Heart transplantation involves large perioperative complications, and can be rejected by the body due to an immune response. Next to that, a shortage of organ donors limits this option. In theory, RM could be a solution for the increasing numbers of osteoarthritis due to an ageing population. Next to this it could prevent organ shortage, intractable spinal cord injury, and many other disorders as well (5;6).

Spectrum of Regenerative Medicine approaches

A wide spectrum of approaches belongs to RM. They all share the goal of regeneration; however they display differential mechanisms of action. These approaches include (stem) cell-based interventions, biomaterial implantation, growth factors, gene transfer, and tissue engineering (2;6;7). A diverse set of *cell-based interventions* exist. The cells can be derived from autologous (the host), allogeneic (same species, different individual), or xenogeneic (from another species) sources. The types of tissue sources vary from embryonic to fetal tissues, as well as adult tissues, such as bone marrow, heart, fat or neural tissue (8). Many of these cells are stem cells: they have the potential to form different type of cells and can self-renew (9). Currently, much research is performed in the potential of induced pluripotent stem (iPS) cells, which are adult stem cells that are re-programmed into pluripotent stem cells which are less differentiated (10). *Biomaterials* can function as a biological or mechanical cue for the development of a tissue (11;12). *Growth factors* are proteins which can stimulate cell proliferation or stimulate matrix production (13). Another large field of applications belonging to RM is *gene transfer* which consists of introducing DNA or RNA in target cells, which then modify, control, inhibit or express a specific target. The DNA or RNA can be directly inserted into the body by using vectors (in vivo gene transfer), or cells can be genetically manipulated ex vivo and then inserted (14;15). *Tissue engineering* is a combination of these approaches: it consists of the triad of cells, biomaterials, and growth factors (16). The term tissue engineering has often been used synonymously to RM, although tissue engineering is also often depicted as a form of RM (1;17). In general, the more extensive the organ or tissue damage, the more complex the approach. When still sufficient tissue viability is available, stimulating endogenous mechanisms in vivo is sufficient, while large damage requires complete organ or tissue building, often outside the body (6;18).

The European Medical Agency has established a novel regulatory category in response to this innovative field: the Advanced Therapeutic Medical Agents (ATMPs). ATMPs are divided into three subtypes: gene transfer medicinal products, somatic cell therapy medicinal products, and tissue engineered products (19). The FDA has a similar type of categories (20). This shows

that RM interventions have been categorized as a separate category, next to pharmaceuticals, devices, and surgery. Nevertheless, some overlap can be found between these: for example, a surgical procedure is necessary for implanting a TE product in the body (21).

Regenerative Medicine in orthopedics

Whereas RM-based interventions are expected to become an important focus in many medical disciplines, orthopedics is one of the leading fields (14;22). The scope of indications for RM in orthopedics is large and diverse. For example, RM technologies are developed for the treatment of degenerative disorders, such as intervertebral disc disease and osteoarthritis (22). Osteoarthritis is characterized by loss of joint cartilage that leads to pain and loss of function primarily in the knees and hips. Especially due to the expected ageing of the population, the burden of osteoarthritis will increase in the future (23). Next to this, low back pain is a major health and socioeconomic problem in Western countries. A recent study into the global burden of disease shows that low back pain ranks highest in terms of disability (24). This demonstrates the need for more effective therapies than current treatments which are typically restricted to pain management followed by end-stage total joint replacement or spine surgery. Especially the effectiveness of the latter for chronic low back pain is seriously doubted (25). Furthermore, RM technologies are developed for (traumatic) defects, such as bone defects, cartilage lesions and meniscal defects (14). Some are also aimed at improving orthopedic surgery, such as spinal fusion, although strictly speaking these applications merely aim to restore instead of regenerate (26).

A landmark RM technique that has been approved for market use is autologous chrondocyte implantation for focal knee cartilage defects (27;28). The translation to clinical practice was developed with scrutiny as many prospective controlled cohort studies were conducted (29). However, the translation of another type of RM intervention, the bone morphogenetic proteins (BMPs) for improving spinal surgery, was less controlled and ethically inappropriate: although these BMPs became commercially available in 2002, it appeared that serious adverse events had been underreported and the research articles contained methodological flaws (30).

Translating Regenerative Medicine from bench to bedside

While these examples show that some RM interventions have been translated from bench to bedside, most of the RM interventions are still in the preclinical phase (14;26;28;31-34). This shows that the translation of discovered RM interventions at the bench to successful application in clinical research and practice is slow and the hype of RM has not been met

(5;6;17;18). This gap between basic sciences, clinical sciences and application also exists in other areas of medical research, and last decade many initiatives have been taken to bridge the gap (35). However, it is suggested that due to several factors, such as the high development costs and the complexity of the approaches, the translation of RM interventions is particularly hampered (15;18). Although quick translation to the clinic is often regarded favorable due to the high medical needs, translation can also be premature and place patients at unnecessary risks, as the case of BMPs demonstrated. Also offering RM interventions via private clinics and outside clinical trials is not necessarily a proper alternative for the slow translation (36;37). At a large scale, patients access these clinics which often offer all kinds of stem cell based interventions that often lack high quality evidence and are overoptimistically advertised on their websites.

Instead, translation of RM interventions from bench to bedside should be facilitated on a responsible manner. Providing moral reflection and ethical guidance on the set-up of clinical studies in this area can stimulate making the leap to clinical studies, as researchers are prepared beforehand on the moral challenges, instead of encountering these during the trial. Furthermore, moral guidance is also important to assist Research Ethics Committees (RECs) in evaluating research protocols involving these emerging technologies.

Ethics and translational Regenerative Medicine

Existing literature on the ethics of translating RM to clinical trials describes the challenges of *early stage* trials (35). Examples of the mentioned challenges are: when to move from preclinical to human research; participant selection (who should be the first to undergo these novel interventions); and gaining adequate informed consent (21;38). Other authors have specifically described the ethical challenges in *stem cell* clinical trials, such as when it is appropriate to move to a first-in-human trial, how to balance risks and benefits, and how to design the trial in terms of the control and endpoints (39-42). Others have mainly described the ethical challenges of translating *tissue engineered products* into clinical trials and society (43-45). Also regulatory bodies and the International Society for Stem Cell Research have provided recommendations on preclinical and clinical aspects of stem cells and tissue engineering (46-52). Furthermore, the ethical challenges of translating *gene transfer* to first-in-human trials have been thoroughly set out (53).

However, in-depth ethical evaluation and normative guidance on these translational challenges is missing, as much of the literature provides only brief considerations or is of descriptive origin. This could also be explained by the dominance of ethical debate on the acceptability of human embryonic stem cells and therapeutic cloning (45). However, a heated debate on the choice for the participant group in the first embryonic stem cell trial for spinal cord injury, demonstrates that challenges such as appropriate participant selection

are also ethically contentious (54-56). Furthermore, professionals in the RM field indicate a lack of normative guidance on challenges like the protection of trial participants, the design of clinical trials, and obtaining adequate informed consent (57). Hence, normative guidance on the translation to clinical research is favorable, for which ethical analysis is a prerequisite. The challenges involved in the translation to clinical research has been called T1 research (35). Next to that, more attention should also be paid to T2 research, which concerns the issues related to the translation to the public sphere, including the societal impacts (35). While there is an evolving ethical debate about the potential societal impacts of RM, the scope should be broadened and enriched (45;58;59).

Also lacking in literature is ethical analysis on the translational ethical challenges that are specific for the orthopedic RM field. On the contrary, the ethics of the cardiovascular and neurological RM field has received more attention (41;60;61). This is surprising as orthopedics is at the front row of RM research (14).

Hence, this thesis adds two main aspects to current ethics literature on translational RM. First of all, in-depth analysis and normative guidance on the main translational ethical challenges in RM is provided. Furthermore, specific ethical guidance for the field of orthopedic RM is provided. Although the field of orthopedics is often used as an example, the guidance is often relevant for other medical domains as well. Particularly, this thesis is relevant for the cardiovascular field as it is used as a comparison with the orthopedic field.

Research aim and scope

The main aim of this thesis is to identify and evaluate the main ethical challenges of translating RM into clinical trials and society, by mainly using the orthopedic field as a case.

In order to fulfill this general aim, the following sub aims were formulated. The first three sub aims mainly *describe* the ethical challenges, while the last three sub aims focus on *evaluation* of some of the key ethical challenges:

- To identify the key ethical issues when translating RM interventions for orthopedic disorders into clinical trials
- To identify the attitudes, opinions, experiences, and expectations of orthopedic biomedical professionals in the translation of orthopedic RM interventions into clinical trials and society
- To identify the similarities and differences between the orthopedic and cardiovascular RM field concerning the ethical issues raised by the translation to clinical trials
- To ethically evaluate whether placebo surgery is acceptable in the context of a RM trial
- To ethically evaluate what constitutes the appropriate comparator in the design of a RM clinical trial
- To ethically evaluate which participant model is most appropriate to select for a RM clinical trial

Research approach

In this thesis ethical-theoretical analysis is combined with empirical research. Empirical work in ethics can have several roles such as describing a particular state of affairs, often in light of a normative question, and/or to gain the moral views and values of the people working in a particular practice (62).
Via the model of wide Reflective Equilibrium (RE), these empirical data can be integrated with other elements, such as moral principles, and (ethical) theories (63;64). RE is a method for moral reasoning. Many philosophers have adjusted the original (narrow) RE model, as developed by Rawls. As the narrow model was limited to the input of ethical theories and the considered judgements of the thinker (i.e. the ethicist), the model was mainly appropriate for developing abstract moral theories instead of providing guidance for concrete moral problems (63). However, for developing guidelines for concrete issues such as in applied ethics, others proposed including non-moral background theories and morally relevant facts (63;64). Also the importance of empirical data, such as the knowledge and experience of practitioners or patients, has increasingly been acknowledged (65). Incorporating their attitudes, opinions, experiences, and expectations allows a broad and rich spectrum of perspectives (62). The RE model is not related to a specific moral theory, such as deontology or consequentialism, but is defined by its coherentism. The thinker goes back and forth between moral principles, theories and empirical data and adjusts these until coherence between these various elements is achieved. In other words, the dynamic reasoning process ends and results in a justifiable moral judgment, view or guidance (62). Achieving coherence means that there is comprehensiveness and interconnectedness between the elements in the model: as many moral principles and values as possible are taken into account and these must be related to each other (62). The reached moral view is a provisionally fixed point, amenable to change depending on new insights and reflection (62).

The empirical research in this thesis consisted both of qualitative, one-to-one interviews with professionals in the orthopedic RM field, and of collaboration with the researchers of a RM clinical trial. The respondents for the qualitative interviews were recruited via the IDiDAS (New Early Therapies for Intervertebral Disc Diseases. Drug Delivery and Augmentation through Smart Polymeric Biomaterials) project which commenced in 2011 and ended in 2014. The IDiDAS consortium, consisting of academic medical centers, a technical university, and industrial partners, aimed to develop a RM intervention for patients with low back pain. This thesis is based on one of the Work packages in this project: ‘Ethics from bench to bedside’ (66). As one of the members of this project, I would join research meetings and have regular conversations with the other members, which would allow gaining insight on the state of affairs regarding the (scientific) developments in RM. In addition, we collaborated with several investigators in the cardiovascular RM field to gain an even wider range of (moral) perspectives and morally relevant facts. In addition, this would allow determining

the similarities and differences between the cardiovascular and orthopedic RM field, which could clarify the morally relevant characteristics of the orthopedic field. This fits with the well-known approach of case-comparison in bioethics and enables enrichment of the moral reasoning process (67).

Another advantage of being embedded in projects at the front lines of orthopedic RM developments is that the ethics research is conducted in parallel with the development of a technology. Hence, as an ethicist I was closely involved with the technology developers, clinical trialists and future applicants (e.g. the surgeons). Being so closely involved in the development allows steering and thereby stimulating responsible translation of RM technologies from bench to bedside. We have the view that the development of a technology can be influenced, which is congruent with the constructivist view on science and technology. According to the constructivist perspective science and technology is affected by societal and political factors, and the other way around. In other words, technology developers and scientists do not operate independently from society but they are mutually constitutive: the values of developers and applicants of technology shape the design of a technology and hence influence society, and the other way around (68). Ethicists can also be actors in this development and thereby could influence the values of technology developers and other stakeholders, and as such could alter the technology.

Structure of thesis

The main chapters of this thesis consist of articles, which have been published or submitted for publication.

The first three chapters provide an overview of the ethical challenges that need to be addressed when translating orthopedic RM into clinical studies and society.

Chapter 2 describes the ethical challenges that arise when setting up a (early) clinical trial for testing RM interventions for orthopedic disorders. This chapter shows that whereas early clinical trials are ethically challenging by nature, certain ethical challenges in these trials will get a new twist due to the characteristics of RM interventions, combined with the characteristics of orthopedic patients. This chapter provides an overview of the key ethical challenges, which are evaluated in **chapters 7**, **8** and **9**.

In **chapter 3** a part of the results of the empirical, qualitative study are presented which are based on one-to-one qualitative interviews with 36 biomedical professionals, working at the front lines of orthopedic RM. The respondents were interviewed on their attitudes, opinions, and experiences regarding the ethical issues in the translation of RM to (early) clinical trials.

In **chapter 4** the other part of the data from the interviews with the biomedical professionals are presented: their attitudes, opinions, and expectations on the challenges when translating RM interventions into society. We describe whether these stakeholders are aware of the potential impacts of emerging technologies, of which societal impacts they are aware, and how they perceive their role in this societal debate.

The next chapters describe the ethical challenges that arise when translating cardiovascular RM interventions into clinical trials.
In **chapter 5** the choices, considerations, and experiences of the investigators of a particular clinical trial with a RM intervention are described: the JUVENTAS trial. This trial investigated the safety and efficacy of autologous bone marrow cells in end-stage vascular patients, in a double-blind placebo-controlled design. Further, the main ethical challenges in this trial are identified and recommendations are provided for researchers setting up similar stem cell trials.
In **chapter 6** one of the key ethical challenges identified in **chapter 5** is further explored: the choice for placebo surgery as a comparator. Since one of the characteristics of RM interventions is their invasive character, the choice for a placebo will require a placebo surgery or injection, also known as sham intervention. By means of a literature search we show, quantitatively, to what extent sham interventions have been used in clinical trials testing cell-based interventions in the field of cardiology. This provides insight into the views on the scientific need and ethical acceptability of sham interventions by medical professionals.

In the last chapters in-depth ethical analysis and normative guidance on two key challenges, as identified in the previous chapters, are provided.

Chapter 7 ethically evaluates the justification of including sham interventions in clinical trials, by means of reflection on existing ethics literature regarding sham interventions.
Chapter 8 concentrates on the ethical evaluation of the appropriate comparator in clinical trials testing RM interventions. This chapter provides comprehensive ethical analysis on the adequate choice of the comparator, including sham interventions.
In **chapter 9** the appropriate choice of participants in RM clinical trials is ethically evaluated. As one of the aims of RM interventions is to prevent disease, it is expected that future RM clinical trials will consider the selection of asymptomatic persons at risk of clinical disease. However, so far the debate on participant selection (based on stage of disease) in the research ethics literature centres around three other participant models. This chapter therefore mainly evaluates the ethical challenges of a fourth participant model: the individual at risk model.

Finally, **chapter 10** looks back at the main findings and looks forward to questions for further research. Further, the contribution of empirical studies to ethical analysis and the role of ethics research in technology development are evaluated. Last, RM technology will be put in a broader societal perspective.

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Chapter 2.

Regenerative Medicine interventions for orthopedic disorders: ethical issues in the translation into patients

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Abstract

Regenerative Medicine (RM) technologies, such as cell therapy, gene transfer and tissue engineering, are expected to move the field of orthopedics into a new era. Now that more and more attempts are underway to translate preclinical research into clinical studies, it is time to proactively discuss the ethical issues associated with first-in-human applications of RM interventions for musculoskeletal disorders. The design and launch of early clinical trials will be ethically challenging due to the specific features of RM in general and the application for musculoskeletal disorders specifically. In this chapter, we identify three sets of ethical issues that need to be addressed when considering initiating early clinical trials: assessment of risks and benefits; designing a study in terms of outcome measures and comparators; and participant selection. These issues are particularly emphasized in RM research that aims to apply these approaches in an early stage of degenerative musculoskeletal disorders.

Introduction

Regenerative Medicine (RM) is an umbrella term for a set of innovative approaches that focus on or utilize the body's natural ability to bring about functional and structural recovery of damaged or degenerated tissues (1;2). Whereas RM-based interventions are expected to become an important focus in many medical disciplines, orthopedics is one of the leading fields (3;4). After all, contrary to the currently used medicines and (replacement) surgery for musculoskeletal disorders that aim at improving symptoms and function, RM-based interventions aim to treat the underlying cause of the symptoms. The relevant RM approaches for orthopedics can be divided into three subtypes (Table 1). The range and amount of possible RM applications in orthopedics is extensive, as every tissue predisposed to damage or degeneration can be a candidate for RM (2) and the prevalence of especially degenerative orthopedic disorders is rapidly growing as a consequence of the aging population (5). The scope of indications for RM in orthopedics is large and diverse, extending from interventions for degenerative disorders, such as osteoarthritis (OA), to the treatment of (traumatic) defects, such as bone defects, cartilage lesions and meniscal defects (3). Whereas some interventions aim more at replacement or repair, such as allogeneic and autologous transplants or grafts, others are heading towards the 'ultimate RM aim' of regeneration through regaining the original healthy tissue, such as early RM interventions in OA. In particular, these interventions for degenerative joint disease, such as OA and intervertebral disc disease (IVDD), or for focal defects that increase the risk for degeneration, may reduce the need for current major surgical (replacement) interventions if degeneration could be prevented or reversed.

While intensive worldwide preclinical research activity into RM interventions for musculoskeletal disorders exists, the design and launch of early clinical trials will be ethically challenging at the same time. Moreover, professionals in the field indicate that clear ethical (and/or regulatory) guidance for clinical trials with RM products is necessary (6).

In this chapter, we identify three sets of ethical issues that need to be addressed when considering the leap from bench to bedside for RM interventions in orthopedic disorders: the analysis and appraisal of risks and benefits; study design in terms of outcome measures and comparators; and participant selection. The ethical issues concern both the initiation of Phase I studies (safety studies) in the strict sense and combined Phase I/II studies (combined safety and efficacy studies).

Table 1. Regenerative Medicine approaches that are relevant for orthopedics

RM approach	Subtypes	Description	Examples	References
Acellular	Growth factors	Shifting tissue homeostasis to the anabolic state by stimulating cells to produce ECM	Basic FGF, BMPs	(7-9)
	Gene transfer	Often combined with a vector (viral or nonviral) to stimulate uptake *Ex vivo* and *in vivo* gene delivery approaches Aim of maintaining high levels of a growth factor or other molecule in the joint	Genes producing a growth factor (e.g., BMP, TGF-β, IL1-Ra), cytokine inhibitors	(10-12)
	Scaffolds	Aim of mimicking the ECM Function and features: mechanical support, regulate cellular activity, biodegradability, biocompatibility and porosity	Natural scaffolds: decellularized ECM scaffolds (xenogeneic, allogeneic or autologous), fibrin, collagen, autograft and allogeneic bone graft Synthetic scaffold: poly-(α hydroxyesters), calcium phosphate, ceramics or bioglasses	(3;13;14)
Cell-based	Autolo-gous/ allogeneic	Injecting cells into diseased tissue, aimed at integration of these cells into the damaged or degenerated tissue	Differentiated stem cells (e.g. chrondocytes), MSCs	(3;15-17)
TE		Traditional triad: scaffolds, cells and growth stimulating factors	*In vitro* TE and *in vivo* TE (in situ)	(13;18-20)

ECM: Extracelullar matrix; MSC: Mesenchymal stem cell; RM: Regenerative Medicine; TE: Tissue engineering

Analysis and evaluation of risks and potential benefits

Acquiring a favorable risk-benefit ratio is an important ethical requirement in clinical research (21). In order to evaluate and increase the acceptability of risks compared with the potential benefits, the risks and potential benefits should first be analyzed (22). Although this should be carefully done in all phases of clinical research, this is challenging by nature in first-in-human studies, since the evidence necessary to analyze risks (i.e., testing in humans) is still missing. This difficulty counts *a fortiori* for RM trials in musculoskeletal disorders, in view of the novelty and complexity of RM products combined with the relatively healthy condition of patients with musculoskeletal disorders.

Analyzing risks

A distinction can be made between risk, uncertainty and ignorance of harm. Risk refers to the likelihood that harm will occur combined with the magnitude of the harm. Uncertainty implies that it is known that there are risks but the probability is unknown. Ignorance implies that it is not known whether there are any risks: 'the unknown unknowns' (23). Risks can be subdivided into several categories: physical, psychological, social and economic (24). First-in-human RM trials for musculoskeletal disorders will particularly raise physical and possibly also psychological risks.

The analysis of physical risks is challenging, due to the novelty and complexity of RM interventions, such as the variability in manufacturing (e.g., in autologous cell-based interventions), the more dynamic aspects (e.g., living cells that interact with a 'living' body) and the long-term impact (e.g., in gene transfer) (25). These features show that some RM products are more complex than traditional drugs or devices (15;25;26). Although relevant animal models can be a powerful tool to estimate risks and benefits, even nonhuman primate studies will not completely represent applications in humans. The fact that the microenvironment is highly important in integrating the RM product into the body complicates the translation of results from preclinical experiments to clinical studies, since even minor differences between humans and animal models may result in different outcomes (26). It is thus possible that both uncertainty and ignorance exist, which will make it difficult to decide when there is enough evidence to test the interventions in humans. Since most RM approaches will be introduced into the body with a minimally invasive surgical technique, some physical risks are implicated *per se*. The magnitude of risk depends on the target tissue: injection in an intervertebral disc inherently creates more risks than intra-articular injection in the knee (27). Furthermore, some interventions, especially with autologous cells, could require extra surgical interventions (e.g., harvesting cells from a cartilage donor site or from bone marrow and injecting them after culturing). Additionally, the magnitude of risk also depends on other (contextual) factors. e.g., whether the risks and uncertainty are delayed, unobservable or irreversible (28). For example, it is quite difficult, if not impossible, to remove stem cells from a human body once they have been transplanted (29).

Psychological harm may also arise due to the anxiety of undergoing an experimental invasive intervention, particularly when combined with experimental gene or cell therapy. In addition, the possible life-long follow-up to analyze long-term safety and efficacy could be burdensome. Finally, the use of cells and/or gene transfer not only has a physiological effect on the recipient, but it could also have cultural, religious, relational or other relevance, depending on the origin of the cells and the degree of manipulation (30).

Analyzing benefits

Benefits in clinical research can be divided into several categories: direct benefits, collateral benefits and aspirational benefits (31). The direct benefits are the benefits for the individual

research participant (i.e., in our context, the (medical) benefits causally related to the applied RM product). Collateral benefits are the benefits not directly related to the product itself, such as psychological comfort due to intensive monitoring. There is a general consensus that collateral benefits should not be taken into account in the risk-benefit ratio, among others, since this could lead to misunderstanding of patients regarding the purpose of the study – the so-called 'therapeutic misconception' (32). Aspirational benefits, also known as social value, include the benefits gained for science and society, which is usually generalizable knowledge and medical benefit for future patients (as opposed to direct benefits for the individual research participant). Early clinical studies are mainly conducted to generate the knowledge that is necessary: to move to the next phase of testing; to motivate further preclinical research by prompting modification of a particular agent; or by being a spin-off for other loosely related areas for future patients (33). Early clinical studies, however, are usually less likely to produce direct benefit for the participant (34). In concordance with the risks, the novelty and complexity of RM in musculoskeletal disorders also make it difficult to determine the benefits of a first-in-human RM trial. In theory, the social value of RM interventions could be particularly high due to its future aim of providing cures instead of symptomatic treatment. However, the (relatively) good clinical results of end-stage treatment in knee and hip prosthesis, for example, will be more difficult to improve than the current surgical treatment for IVDD (35-37).

Evaluation of risks and benefits: in search of proportionality

After analysis of the risks and potential benefits, the next step is to evaluate whether these are in reasonable proportion. What benefit (if any) of first-in-human trials can justify the risks and burden for individual research participants? Since patients with musculoskeletal disorders are a relatively healthy patient population (no heightened mortality rate), the proportionality of the risks and uncertainty versus the expected benefits becomes a salient issue. To increase the likelihood of achieving a favorable balance of benefits over risks, efforts should be made to minimize the risks and to maximize the benefits as much as possible. Minimizing risks and controlling uncertainty could be achieved through intensive monitoring during the study, the choice of the comparator, by appropriate participant selection, the choice of the RM compound (e.g., level of complexity), the method of implantation (e.g., size of needle) and by increasing the reliability and validity of preclinical evidence (e.g., by using large animal models, despite the earlier mentioned limitations), among others (33). Maximizing benefits could be achieved by identifying or developing a clinically relevant outcome measure, by carefully choosing a comparator, by appropriate participant selection and by valid preclinical testing, among others. However, one should be aware that the avenues of minimizing risks and maximizing benefits do not necessarily have to be compatible with each other.

Study design: appropriateness of outcome measures and comparators

Low-quality scientific research is ethically challenging because it exposes patients to risks and burdens while generating few or no scientifically valid results. However, the efforts of increasing scientific validity and protecting participants could interfere or even conflict with each other (21). To explain this tension in the musculoskeletal RM field, we will concentrate on two aspects that should be considered when designing a combined Phase I/II study: the choice of the outcome measure and the choice of a comparator.

Choice of outcome measures

The choice for the type of outcome measures is of ethical relevance because it partially determines the value of a study and (therefore) influences the risk-benefit ratio. In particular, when patients with a degenerative musculoskeletal disorder are included, the choice of an outcome measure is more difficult due to the absence of a clear hard end point. This is due to the fact that clinical symptoms in degenerative musculoskeletal disorders (e.g., pain and functional disability) are not fully correlated with current diagnostic tools that assess functional or structural condition, such as imaging (38-42). Furthermore, the working mechanisms of the new and complex RM interventions, which are aimed at regeneration, are not yet fully elucidated, thus preferably requiring a long follow-up time (25). Therefore, the difficulty in correlating clinical symptoms with current diagnostic tools and the novel character of RM interventions make the choice of outcome measures challenging.

Choice of comparator: standard of care or placebo surgery?

Standard of care as comparator

Since current therapies for musculoskeletal disorders do not aim at regeneration, RM could, in theory, be superior to any existing medical therapy (43). However, the safety and efficacy of a RM intervention should first be assessed against a proven and/or effective comparator: the standard of care. There is a strong consensus that patients should not be withheld an intervention that provides a net medical advantage, which implies that any experimental RM intervention should first be compared against the standard of care, if available (44). Therefore, the technique of autologous chondrocyte implantation for focal articular damage was compared in several studies with standard-of-care interventions, such as microfracture and osteochrondal graft (16). For OA and IVDD, for example, no therapies that prevent or reverse the progress of degeneration are currently available. Therefore, it is questionable whether there is a standard of care available as a comparator for many RM interventions (45).

Placebo surgery as comparator

For those musculoskeletal disorders for which no standard of care is available that provides a net medical advantage, a placebo could be a suitable comparator. Placebo could be considered an option when there is considerable social value, when placebo is methodologically necessary or desirable and when the risks are minimized and in proportion to the potential benefits (46). As the subjectivity of clinical symptoms is high and no clear hard outcome measures are available in degenerative orthopedic disorders, assessing the amount of placebo effects is preferable for scientific validity. RM products will usually have to be implanted via minimally invasive surgery or injection. If placebo is used, placebo surgery/injection, also known as sham surgery/injection, is required. Placebo or sham surgery is both scientifically and ethically contentious. Although the effect of placebo surgery has been disputed, other studies have demonstrated placebo effects (47). Furthermore, placebo surgery is more controversial than oral placebo medication, since sham procedures will always involve harm, mainly due to anesthesia and the creation of a wound. As a consequence, a placebo intervention creates an ethical dilemma between maximizing the scientific validity (and thus the social value) of a study and minimizing the risk to participants. In the literature, the debate regarding the ethical acceptability of sham surgery has, thus far, mostly concentrated on placebo-controlled trials of fetal tissue transplantation for Parkinson's disease and on an arthroscopic surgery trial for knee OA (47-49). The ethical acceptability of a placebo is co-determined by the associated risks of the procedure. Minimally invasive RM sham interventions might not expose participants to excessive risk or discomfort, especially if anesthesia is not necessary and only minor wounds are created. For example, in studies assessing the safety of gene transfer and growth factors in OA, a saline or lactose solution was delivered via a minimally invasive injection and no anesthesia was required (11). The risks of these placebo interventions might be compared with the (widely accepted) risks for volunteers in Phase I trials and diagnostic studies (46). Furthermore, patients with musculoskeletal disorders are often relatively healthy patients without comorbidities and have fewer surgically caused risks compared with patients with organ diseases, such as cardiovascular diseases. This implies that the acceptability of placebo surgery is also affected by the extent of the surgery and the relatively healthy condition of patients with musculoskeletal disorders.

Participant selection

The choice of the most appropriate population to answer a research question is of paramount importance and has been subject to dispute in some RM studies in the past (50;51). When investigating RM interventions for musculoskeletal disorders, participant selection is particularly challenging, due to the risks and uncertainty of RM approaches, the difficulty of diagnosis and prognosis (especially for IVDD), the relatively effective (end-stage)

symptomatic options and the relatively healthy condition of patients. Several models of participant selection exist (33).

Healthy volunteer model

From an orthopedic perspective, healthy volunteers are persons without any subjective complaints and without any 'objective' abnormalities, such as the first signs of OA on imaging. In Phase I drug trials, healthy volunteers are often included to assess safety, since they can better tolerate adverse effects in general (50). As previously mentioned, due to the novel, complex and surgical character of RM interventions, the risks and uncertainty for these participants are relatively high. The level of risk could be compared with highly toxic drugs, such as chemotherapeutics. Therefore, the choice of healthy volunteers does not seem likely to be an ethically acceptable first step in RM research.

Stable patient model

Early-stage disorder

We refer to stable patients in orthopedics as patients with an early stage of degeneration that has led to symptoms and minor 'objective' abnormalities. If degeneration proceeds, these patients could become eligible for future symptomatic therapies, such as knee prosthesis, spinal fusion or disc replacement. The RM field is interested in developing interventions for early-stage disease because early RM interventions could prevent the need for symptomatic strategies, such as replacement or fusion. Furthermore, many RM interventions are most effective when applied to a microenvironment in which the cell viability and nutrient supply is still present (i.e., early-stage disease) (13;18). However, it may be difficult to identify early-stage patients because there is debate regarding how to define and detect degeneration, especially for IVDD (40), in contrast to, for example, a focal cartilage defect or fracture. In addition, not all patients in early-stage disease will proceed to the advanced stage of the disease. Stable early-stage patients therefore run the risk of unnecessary treatment, thereby receiving a potentially unsafe intervention that could worsen the function of the joint or spine. Furthermore, one could question the acceptability of allowing these patients to undergo a possibly risky and uncertain experimental treatment, since the current (end-stage) symptomatic treatments are quite safe, effective and satisfying, especially in knee and hip prosthesis. However, for younger patients who run a high risk of needing a prosthesis, this option seems less attractive owing to the higher revision rate (35). Therefore, it seems to be most fair to include stable patients in a study on RM interventions when safety has already been established.

Patients at risk of developing musculoskeletal disease

The subgroup of stable patients that could be eligible for conducting early clinical studies is at high risk of developing degeneration. For example, patients who are elected for surgery for disc herniation or spinal fusion generally have an increased risk of disc degeneration at adjacent motion segments (52). Although the chance of developing such advanced adjacent pathology is high, a complicating aspect could be that it is hard to determine whether an effect could be attributed to the RM intervention or is a result of treatment at the primary level.

'Oncology model': patients with an advanced-stage disorder

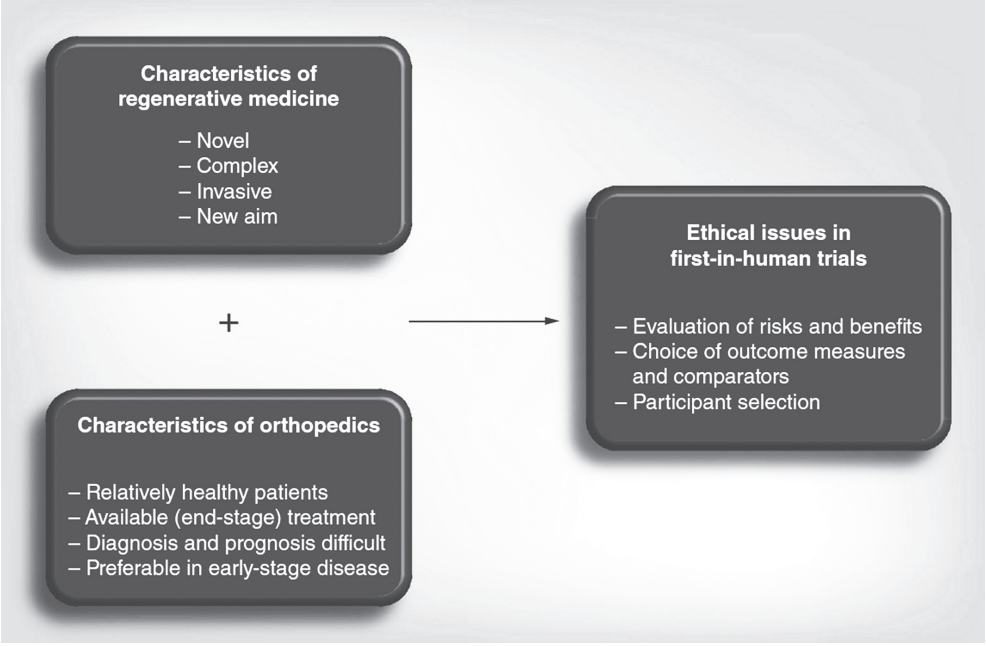
Whereas the so-called 'oncology' model usually refers to terminally ill patients, in this context, we are referring to chronic/advanced-stage orthopedic patients that are eligible for joint arthroplasty or spinal fusion or are deprived of further therapeutic options. The disease is in a late stage of progression: the original tissue, such as articular or intervertebral disc cartilage, is hardly present any more and has been replaced by scar/fibrous tissue. An important difference with oncology patients is that the mortality rate is not affected and that patients are not completely therapeutically refractory, since the option of replacement surgery is still open. To assess the safety (and potential efficacy) of RM interventions, these patients might be most appropriate to include as a first step, as these patients cannot lose much more functionality, unless the consequences of the intervention affect the surrounding and remaining tissue to such an extent that, for example, placing a prosthesis becomes more difficult. However, one drawback is that the potential benefits for these patients are lower due to the less suitable microenvironment for many RM interventions (7;18).

Conclusion

We have identified three sets of ethical issues that need to be addressed when considering initiating early clinical trials in the rapidly developing field of RM for musculoskeletal disorders. Whereas first-in-human trials are ethically challenging by nature, certain ethical issues will get a new twist due to the characteristics of RM and the orthopedic population (Figure 1). The novel, invasive interventions currently under development are aimed at a relatively healthy study population for whom (end-stage) symptomatic treatments (e.g., prosthesis, microfracture and autografts) often exist. They therefore do not fall in the 'no option' category that is often enrolled as a target population in Phase I studies. In particular, first-in-human studies in patients with degenerative musculoskeletal disorders are both technically and ethically challenging, since diagnosis is difficult due to the absence of good diagnostic tools that correlate with symptoms. This is in contrast to bone fractures or cartilage defects, which are much less influenced by psychosocial factors and are easier to objectify by imaging. In

addition, when applied in early-stage disease, patients with degenerative disorders will be offered a potentially risky intervention that could worsen the disorder, despite the fact that they might not progress to an advanced disease stage and might have had other symptomatic treatment options.

Figure 1. Ethical issues raised by Regenerative Medicine interventions for orthopedic disorders



Future perspective

Thoughtful and timely consideration regarding the design of early clinical studies for RM interventions for musculoskeletal disorders is important and urgently needed. The initially negative experiences with gene therapy can serve as a warning for cautious and responsible innovation in RM. While the RM field is already heading towards applications in early-stage diseases and progress is being made in developing early (genome) screening techniques to predict the risks for diseases, interventions for early-stage musculoskeletal disorders will be particularly challenging. In addition to the ethical aspects discussed in this chapter, the regulatory frameworks for the different RM interventions should be taken into account, as these can answer some of the ethical issues, but can also raise novel ethical concerns. The current controversy surrounding metal-on-metal hip implants, which are regulated as devices, shows that regulatory approval does not necessarily solve ethical issues. Orthopedic

RM is a promising and exciting new field with the potential to dramatically change the field of orthopedics, but further interdisciplinary research and ethical debate are needed in order to translate these RM interventions from the bench to the bedside in a morally sound way.

Executive summary

Analysis and evaluation of risks and potential benefits

Acquiring a favourable risk-benefit ratio is challenging by nature in first-in-human studies since the evidence necessary to analyse risks - testing in humans - is still missing.

This difficulty counts *a fortiori* for RM trials in musculoskeletal disorders, in view of the novelty and complexity of RM products combined with the relatively healthy condition of patients with musculoskeletal disorders.

Study design: appropriateness of outcome measures and comparator

The difficulty in correlating clinical symptoms to current diagnostic tools and the novel character of RM interventions challenge the choice for outcome measures.

Patients should not be withheld an intervention that provides net medical advantage, which implies that any experimental RM intervention should first be compared against the standard of care, if available (such as for focal cartilage defects).

Since in degenerative musculoskeletal disorders the subjectivity of clinical symptoms is high and no clear objective outcome measures are available, assessing the amount of placebo effects is preferable for scientific validity. RM interventions will require placebo (sham) surgery which creates new ethical concerns, compared to placebo pills.

Participant selection

Participant selection in early clinical studies for degenerative musculoskeletal disorders is particularly challenging due to the risks and uncertainty of RM approaches, the difficulty of diagnosis and prognosis (especially for IVDD), the relatively effective (end-stage) symptomatic options and the relatively healthy condition of patients.

Concluding remarks

Whereas first-in-human trials are ethically challenging by nature, certain ethical issues will get a new twist due to the characteristics of RM interventions, combined with the features of orthopedic patients.

Especially application of RM in early stage degenerative musculoskeletal disorders will raise challenges.

Further interdisciplinary research and ethical debate is needed to translate these RM interventions from bench to bedside in a morally sound way. Also the regulatory frameworks should be taken into account.

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Chapter 3.

Ethical implications of Regenerative Medicine in orthopedics: an empirical study with surgeons and scientists in the field

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Abstract

Background context Regenerative Medicine (RM) interventions, such as (stem) cell transplantation, scaffolds, gene transfer, and tissue engineering, are likely to change the field of orthopedics considerably. These strategies will significantly differ from treatments in current orthopedic practice, as they treat the underlying cause of disease and intervene at a biological level, preferably in an earlier stage. Whereas most of the RM interventions for orthopedics are still in the preclinical phase of research, the number of clinical studies is expected to increase rapidly in the future. The debate about the challenging scientific and ethical issues of translating these innovative interventions into (early) clinical studies is developing. However, no empirical studies that have systematically described the attitudes, opinions, and experiences of experts in the field of orthopedic RM concerning these challenges exist.

Purpose The aim of this study was to identify ethical issues that experts in the area of RM for musculoskeletal disorders consider to be relevant to address so as to properly translate RM interventions into (early) clinical studies.

Study design/setting In-depth qualitative interviews were conducted with 36 experts in the field, mainly spine surgeons and musculoskeletal scientists from The Netherlands and the United Kingdom.

Methods A topic list of open questions, based on existing literature and pilot interviews, was used to guide the interviews. Data analysis was based on the constant comparative method, which means going back and forth from the data to develop codes, concepts, and themes.

Results Four ethical themes emerged from the interview data. First, the risks to study participants. Second, the appropriate selection of study participants. Third, setting relevant goal(s) for measuring outcome, varying from regenerating tissue to improving well-being of patients. Finally, the need for evidence-based medicine and scientific integrity, which is considered challenging in orthopedics.

Discussion The overall attitude toward the development of RM was positive, especially because current surgical treatments for spine disorders lack satisfactory effectiveness. However, efforts should be taken to adequately address the ethical and scientific issues in the translation of RM interventions into clinical research. This is required to prevent unnecessary risks to study participants, to prevent exposure of future patients to useless clinical applications, as well as to prevent this young field from developing a negative reputation. Not only will the orthopedic RM field benefit from ethically and scientifically sound clinical studies, but the rise of RM also provides an opportunity to stimulate evidence-based practice in orthopedics and address hype- and profit-driven practices in orthopedics.

Introduction

Regenerative Medicine (RM) is a new, interdisciplinary, innovative field of complex interventions focused on biologically repairing, replacing, or regenerating damaged or diseased tissues (1). Potential orthopedic RM approaches involve, among others, (stem) cell transplantation, scaffolds, gene transfer, and tissue engineering (2). These approaches could be used for treating degenerative disorders, such as intervertebral disc disease, or for improving surgical treatments, such as spinal fusion (2). Most of the RM interventions for orthopedics are still in the preclinical phase, although some early clinical (including first-in-human) studies have commenced and several have been completed (3-9). Today only one orthopedic RM treatment, specifically the treatment for focal knee cartilage defects, is approved for market use (10;11). As the amount of (early) clinical studies in this field is expected to rapidly expand in the near future, it is time to proactively discuss the scientific and ethical issues involved in the translation of preclinical research into clinical studies. For innovative technologies, like RM, the traditional ethical benchmarks for conducting clinical research proposed by Emanuel et al. (12) require refinement. In particular, the decision of when translation into first-in-human studies is justified is challenging, because these complex novel approaches have never been applied in humans before. Additionally, the combination of the specific characteristics of RM with the characteristics of orthopedic patients implies that new challenges will arise (13). Specific characteristics of RM include complexity, new aims (compared with drugs and devices), and early-stage effectiveness, whereas orthopedic patients are characterized by their relatively healthy status (in the sense of having a nonlethal disorder) and the strong influence of psychosocial factors. Empirical ethics research provides factual information about the state of affairs in a specific practice and identifies the attitudes, opinions, and experiences of relevant actors. By combining experts' attitudes, opinions, and experiences with ethical theories and principles, a coherent view on the ethical issues in orthopedic RM research can be formed (14). The aim of this study was to identify the ethical issues experts consider necessary to address before translating RM interventions into clinical research, and to combine the mentioned issues with our own ethical analysis.

Materials and methods

Design

Qualitative research aims to generate rich, in-depth understanding of attitudes, opinions, and experiences of individuals in a specific context or practice (15;16). Data are primarily gathered from an interview design, and data analysis is largely inductive, which allows meaning to emerge from the data rather than the more deductive, hypothesis-centered approach of quantitative research (15). Therefore, the attitudes, opinions, and experiences (when available) of experts regarding the ethical issues in translational clinical RM research

for musculoskeletal disorders were examined by means of qualitative interview design (16;17). This study was conducted as part of the Dutch BioMedical Materials–funded consortium IDiDAS (New Early Therapies for Intervertebral Disc Diseases. Drug Delivery and Augmentation through Smart Polymeric Biomaterials). IDiDAS involves four academic medical centers, one technical university, and industrial partners and is in the preclinical phase of developing RM interventions for the treatment of intervertebral disc disease. In our work package ethics, IDiDAS is used as an example to identify ethical issues that will arise in translating RM interventions for orthopedic disorders from bench to bedside.

Respondents

Respondents were recruited using the network of the IDiDAS consortium and by following recommendations from the interviewees (so-called snowball sampling) (18). Inclusion criteria were that the respondent is involved in (pre)clinical orthopedic RM research, and/or has experience with conducting clinical research or practice in degenerative musculoskeletal disorders. These latter respondents were included to provide insight in the general challenges in conducting orthopedic research. One-on-one, in-depth interviews were mainly held with scientists working at the bench in orthopedic RM and with surgeons in different areas of orthopedic surgery (primarily spine) who were involved in the field of RM or orthopedic research (Table 1). We aimed to collect a range of attitudes, opinions, and experiences as wide as possible, termed contrast maximization, by selecting respondents of different professions, specializations, and nationalities (16). In total, 36 interviews were conducted; 12 people did not respond and 4 rejected the invitation. Recruitment was ended when saturation was reached (i.e., when no new thematic content was found) (19).

Interview strategy

The interviews were conducted by S.N. between April and November 2012. The interviews lasted between 30 and 75 minutes and most interviews took place at the workplace of the respondent. Five interviews were done by telephone. A topic list, based on existing literature and pilot interviews, was used to guide the interviews but respondents were able to add other aspects (Supplemental file: Topic List). Questions about the translation from preclinical research to first-in-human studies, and from clinical studies to society were incorporated. Typically, for qualitative interview design, the topics evolved during the interviews. Hence, not all topics were systematically discussed in all respondents in the same way. In this article, we report the results about the issues raised in the translation into early clinical studies. The description of three possible future RM interventions for different types and stages of orthopedic disorders (depending on the specialization of the respondent) were often used as a tool during the interviews (Supplemental File: Topic List). Although only a small number of early clinical studies and applications exist, many respondents (n = 13) had experience with

Table 1. Respondents' characteristics

Respondents	**N = 36**
Sex	
Male	**31**
Female	**5**
Nationality	
Dutch	**23**
English	**11**
German	**1**
Swiss	**1**
Profession	
Surgeon	**20**
Basic scientist	**14**
Research funder	**2**
Specialization of surgeons	
Spine surgery	**10**
Knee surgery	**2**
General surgery	**6**
Hand surgery	**1**
Veterinary surgeon	**1**
RM[a] research experience	
Preclinical research	**26**
Clinical study	**13**
No RM experience, but experience in orthopedic research	**9**

clinical research or applications in orthopedic RM. These respondents were also asked about their experience with conducting clinical studies in this field.

Data analysis

The interviews were audiotaped, transcribed verbatim, and stored anonymously, after permission was given by respondents. Data analysis was based on the constant comparative method, which involves going back and forth from the data to develop codes, concepts, and themes (16). S.N. independently coded the full transcripts by labeling units of texts that referred to one or more topics relevant to the study purpose. Coding was done with NVivo 8 software (20). One member of the research team, A.B., read the full transcripts with coding and J.v.D. and A.B. checked the codes for consistency. The codes were adjusted by comparison across transcripts and by discussion with all authors. After consensus on coding was reached, the codes were developed into higher-order concepts and themes to provide a framework for coding subsequent transcripts. Subsequently, the themes for discussion were

discussed with all authors. We did not show which percentage or number of respondents expressed a certain opinion, as quantification does not correspond with the aim and method of qualitative research (15).

Results

We identify four main themes emerging from the interviews regarding the translation of RM interventions into early clinical research.

Theme 1. Keep risks of RM interventions low

Many respondents expressed concerns about RM technology because it exposes study participants to possible harms. Most experts highly favor the ‘‘first do no harm’’ principle, especially because orthopedic disorders are mainly quality of life-disorders, whereas the risks of RM are often unknown. Experts were concerned about potential serious adverse events of RM approaches, especially the increased risk of cancer. They pointed to evidence on bone morphogenetic proteins (BMPs) for spinal fusions, aimed at regeneration, which showed tumor formation could be a possible side effect. Risk-averse attitudes were especially displayed for experimental interventions in the intervertebral disc, because both the magnitude and the probability of harm were regarded to be higher than for interventions in synovial joints, among others, due to the anatomy of the spine and the location near the spinal cord.

Theme 2. Consider carefully which participants are most appropriate

Many respondents brought up two issues related to the choice of the most appropriate participants for (early) clinical studies in orthopedic RM: the uncertainty around the relationship of degeneration and symptoms, and the appropriate stage of intervening.

Uncertainty around relationship of degeneration and symptoms

Many emphasized that for research to be relevant, a clear diagnosis and natural history are needed to draw accurate conclusions about the effect of the intervention. In almost every interview, the point was raised that injecting regenerative compounds in patients with a degenerative orthopedic disorder is currently doubtful to recommend, as controversy exists on the relationship between degenerative changes and patients’ clinical symptoms. Many surgeons mentioned that this correlation is disputable, because the exact origin of pain is unclear and psychosocial factors have a considerable influence. Many mentioned that the diagnosis of osteoarthritis in peripheral joints, compared with disc degeneration, is less controversial because more diagnostic instruments, such as arthroscopy, are available.

Appropriate stage of intervening

Furthermore, most respondents speculated about the most appropriate stage of a degenerative musculoskeletal disorder for enrolling patients in a clinical study. For degenerative disorders, experts mentioned several groups that could be eligible for intervening with RM: asymptomatic persons with high risk of degeneration, symptomatic patients with minor degeneration (early-stage patients), and symptomatic patients with severe degeneration (advanced stage patients). Some respondents favored including early-stage patients because these belong to the group in which highest efficacy could be achieved. However, the inclusion of this group of patients is also complicated because of higher risks involved.

Theme 3. Setting the goal(s) for measuring outcome: tissue regeneration versus improving patients' well-being

Most experts noticed that the choice of outcome measures in clinical studies for RM interventions is challenging. Actually, setting the goals of a clinical RM study is closely related to setting the goal of RM. Many experts noticed that the field should deliberate about what RM should ultimately strive for: tissue regeneration or improving symptoms and well-being of patients. Most respondents expressed that it is most important that outcome measures reflect well-being of participants, because this should be the goal of medical research. Some warned that a narrow focus on regeneration of tissues probably will not benefit patients, because of the difficulty of correlating radiological signs of degeneration with experienced pain (Theme 2). Especially scientists, however, were convinced that regeneration also should be used as an outcome measure in the design of clinical studies, to gain scientific knowledge about the working mechanism of the interventions.

Theme 4. Conduct evidence-based medicine and stimulate (scientific) integrity

The experts expressed concerns about a lack of both evidence-based medicine (EBM) and of (scientific) integrity in orthopedic surgery. These aspects could also negatively affect a proper research climate for researching RM interventions.

Evidence-based medicine in surgery

To avoid a lack of evidence-based practice when RM interventions are introduced in health care, the experts recommended RM research to be developed carefully, with adequate basic science, preclinical research, pilot studies and, preferably, randomized controlled trials (RCTs). The most mentioned reasons that hamper EBM practice in surgery were related to the (traditional) culture and nature of orthopedic surgery. Some experts mention that the lack of EBM is partially caused by the culture of a ''trial-and-error'' approach in surgery. In addition, the attitude of orthopedic surgeons was thought to be, at least partly, causal to

hampering the development of an EBM practice: the eagerness to operate (''finding a quick fix'') and experiment with new interventions while no proper evidence is available. Some UK respondents mentioned that the attitude of easily performing surgery is more widespread there, compared with The Netherlands. Furthermore, the free market system in some Western countries, as well as the preference of many patients to be operated, would also make surgeons more willing to operate. Others, however, mentioned that EBM is lacking as surgical trials are more difficult to perform than drug trials, for example, as a surgical trial is more expensive and logistically more challenging. For RM specifically, the different ''languages'' of scientists and surgeons could hamper the development of proper clinical studies.

(Scientific) integrity in orthopedic research

The experts worried about the hype of RM, which is partially caused by the drive for profit of industries and by the high expectations of researchers for providing a definite cure for diseases that are now intractable. They were worried that these secondary interests cause a lack of scientific integrity in RM research. One of the consequences could be that it leads to improper design of clinical studies. Many observed that a consequence of the hype and profit drive in orthopedic surgery is that interventions are commercialized too soon without proper research beforehand.

Discussion

It is expected that the use of RM interventions in orthopedics will rapidly increase in the near future. Although experts in the orthopedic RM field welcomed the increasing (preclinical) research into RM interventions for orthopedic disorders, they addressed four challenges in the translation to clinical research, especially for degenerative musculoskeletal disorders (13). It was not surprising that the issues of acceptability of risks and participant selection were mentioned by the respondents, as we have earlier identified these aspects as being challenging in orthopedic RM (13). Especially challenging is the uncertainty of risks owing to the relative novel and complex character of RM, while orthopedic patients are relatively healthy. Furthermore, in the early trial phases, the choice for the appropriate participant group will mainly depend on the acceptability of risks and uncertainty in relation to the expected scientific knowledge (as individual benefits are hardly expected). In the end, advanced-stage patients are probably most eligible, because these patients have least functionality to lose when harms occur, and also diagnosis in these participants is easier (21-23). The mentioned aspect of the need to discuss the aim of RM research is interesting, as this issue has hardly been expressed in the ethical debate before. The responses show that some favor clinical studies that aim at outcome measures capturing well-being so as to inform clinical practice, whereas others favor gaining scientific knowledge about the mechanism of action of RM. In a developing a field like RM it is important to combine

both aims, as is also proposed in the ''translational model of value.'' Whereas especially in later trial phases a focus can be placed on clinical outcome measures (progressive value), the value of a study should be enhanced by also collecting information to promote further (pre)clinical studies; for example, by collecting tissue or tracking cells to understand the working mechanism (also called iterative, collateral, or reciprocal value) (24). This last aspect also ensures that negative findings on clinical outcomes, which can be expected in these first-in-human studies due to its novelty and complexity, are valuable (25;26). Next to the challenge of establishing valuable goals for RM research, a pertinent issue is how to obtain valid and reliable research results in the current context in which orthopedic surgery lacks a strong tradition of EBM practice (27-29). As also mentioned by the respondents, the lack of evidence-based practice in orthopedic surgery complicates the achievement of an evidence-based culture in RM. In surgery, pathophysiological theories, mechanism of disease, and reliance on clinical experience have historically dominated the basis for treatment of individual patients (27). This paradigm still remains, although the need for more rigorous evaluation, such as RCTs, for surgical interventions is increasingly being acknowledged (29-31). Many reasons for the current reliance on theory and individual experience instead of on large empirical studies exist, ranging from the surgical ''culture'' (e.g., the importance of personal prestige) to methodological and practical issues that complicate RCTs in surgery (27;29). The methodological and practical issues are, for example, the learning curve and variability in experience between surgeons of a new surgical technique, high efforts required for recruitment and treatment of patients, difficulties of blinding the surgeon and the patient, and the problems of crossover when one of the alternatives is available elsewhere as a standard care (27;29-33). These difficulties in designing RCTs for surgical interventions are valid, but not all are applicable to RM. It is likely that under certain circumstances, RCTs for RM approaches are required and feasible. Furthermore, it is interesting that the stakeholders are worried that in their field the role of commerce in surgical research and clinical practice causes conflicts of interest that could negatively affect the integrity of researchers and the scientific validity of clinical studies (34-36). The BMP turmoil has shown that conflicts of interest can both lead to adverse events being underreported and the design being methodologically flawed (37;38). Additionally, profit-driven research may result in novel interventions being introduced, although there is relatively scarce evidence and later shown to be less promising than expected (39). This hype cycle is not only caused by industry, but also by various other parties, such as universities, valorization-driven government bodies, and funding bodies (40). Especially RM interventions are at risk of being pushed onto the market too early because they are often developed by small companies and sponsored by venture capitalists, which need a quick return on investments (38;41;42). To promote a research climate that facilitates the gain of robust, valid, and ethically obtained results, several measures could be taken, such as the disclosure of conflicts of interest in reported studies, and improving the review of research protocols and editorial review of manuscripts (34;42;43). Furthermore, incorporation of education about RM, surgical clinical studies, and ethics in the specialization trajectory

to orthopedic surgeon is important. Additionally, research programs should stimulate collaborations between scientists (e.g., biologists, engineers) and orthopedic surgeons to promote translational research. Our study has some limitations. A weakness of this study may be that many of the clinicians interviewed were not conducting RM research. These clinicians might not be sufficiently aware of the latest developments and characteristics of the different types of RM to be able to representatively convey current facts and knowledge, such as concerning risks. However, assessing risks cannot be objective, as the analysis and evaluation depend also on subjective elements and have social and cultural dimensions (44). Another potential weakness is that this study is limited to mainly two nationalities of respondents, and that mainly spine surgeons were interviewed. However, as the experts varied highly with regard to profession, a diversity of attitudes, opinions, and experiences was expected. Another limitation is that financial and other conflicts of interest could have influenced the responses of interviewees, and that these were not explicitly described in this study. However, these respondents are at the same time also the ones who have the most experience with the topics in this study. General characteristics of the respondents are provided in the Table 1, but conflicts of interest were not described explicitly so as to ensure the anonymity of respondents.

Concluding remarks

Regenerative Medicine is a new, innovative field of complex, biologically based interventions that is expected to change the orthopedic field considerably in the future. It is necessary to ensure that these interventions are, in the end, aimed at patients' well-being, while at the same time adding to biological knowledge. Regenerative Medicine could form an impetus to address and improve evidence based practice in orthopedics, and to stimulate responsible innovation and collaboration among industry, researchers, surgeons, and other partners. Not only the orthopedic RM field alone will benefit from proper efforts to promote ethically and scientifically sound translation into clinical research, but also the orthopedic field as a whole.

Acknowledgments

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Supplemental File: Topic List

Topic List for physicians

Personal traits

Name, age, short professional (specialisation) history

Regenerative Medicine and orthopedics

Are you experienced with RM in orthopedics?

If yes:
Which experience do you have? Could you tell me what kind of patients you have treated?
What do you think is the aim and added value of RM in orthopedics?
Which are suitable and feasible patients? Which musculoskeletal disorders?
What do you think are the differences, advantages and disadvantage in comparison with other therapies?

If no:
What are your expectations of RM in orthopedics?
What do you think is the aim and added value of RM in orthopedics?
Which types of RM do you know? Do you have examples within orthopedics?
What are suitable and feasible patients? For which musculoskeletal disorders?
What do you think are the differences, advantages and disadvantage in comparison with other therapies?

Clinical Study

How do you think a study should be set up or if experienced, how was the set-up of the trial, or what would be your ideas about the set-up of trials, related to the below cases?

- Preclinical research, how much must be known to initiate trial?
- Outcome measures: endpoints, time of follow-up
- Inclusion of type of patients for safety and efficacy: stable, end stage, volunteers
- Expected risks of surgery/product/social/psychological/others
- Expected benefits: social value and individual benefits
- Weighing risks and benefits
- Placebo surgery: disadvantages and advantages, methodological and ethical, alternatives?
- Informed consent

Case 1.
Minimally invasive injection with a gel to stop degeneration of disc or to induce regeneration. Early in the disease process in patients with minor complaints, far before spinal fusion would be an option.

Case 2:
Injectable gel with bone growing factor (e.g. stem cells, BMP) as an alternative for autologous bone for spinal fusion surgery.

Case 3:
Injectable controlled release system to treat discs at risk and prevent degeneration. Injection before any large abnormalities exist and the patients do not have any complaints.

Society

What do you expect that RM can have for consequences for society if applied in the clinic?
Do you have an idea about for whom the RM technique should be available and be paid?
Do you regard RM as a therapy, enhancement or as prevention?
Do you think RM will be a medical or non-medical intervention?
Do you think the view of ageing might be affected by RM?
Do you think that these interventions will lead to early diagnosing and treatment? Will this influence how we will appreciate health and sickness?
Do you think moral problems could exist related to the origin of materials?

What do you know about the role of industry in RM applications and development?

Do you know other professionals suitable for interviewing?

Topic List for researchers

Personal traits

Name, age, short professional history

Regenerative Medicine and orthopedics

Which experience do you have with RM in orthopedics?
With what kind of RM techniques do you work?
Which types of RM do you distinguish? Which is most promising do you think? Or which is already in the clinic?
What do you think is the aim and added value of RM in orthopedics?
What are suitable and feasible patients? Which musculoskeletal disorders?
What do you think are the differences, advantages and disadvantage in comparison with other therapies?

Translation to Clinical Study

How do you think a trial should be set up or if experienced, how was the set-up of the trial, or what would be your ideas about the set-up of trials, related to the below cases?

- Preclinical research, how much must be known to initiate trial?
- Outcome measures: endpoints, time of follow-up
- Inclusion of type of patients for safety and efficacy: stable, end stage, volunteers
- Expected risks of surgery/product/social/psychological/others
- Expected benefits/social value
- Weighing risks and benefits
- Placebo surgery: disadvantages and advantages, methodological and ethical, alternatives?

Case 1.
Minimally invasive injection with a gel to stop degeneration of disc or to induce regeneration. Early in the disease process in patients with minor complaints, far before spinal fusion would be an option.

Case 2:
Injectable gel with bone growing factor (e.g. stem cells, BMP) as an alternative for autologous bone for spinal fusion surgery.

Case 3:
Injectable controlled release system to treat discs at risk and prevent degeneration. Injection before any large abnormalities exist and the patients do not have any complaints.

What do you know about the role of industry in RM applications and development?

Translation to Society

What do you expect that RM can have for consequences for society if applied in the clinic?
Do you have an idea about for whom the RM technique should be available and be paid?
Do you regard RM as a therapy, enhancement or as prevention?
Do you think RM will be a medical or non-medical intervention?
Do you think the view of ageing might be affected by RM?
Do you think that these interventions will lead to early diagnosing and treatment? Will this influence how we will appreciate health and sickness?
Do you think moral problems could exist related to the origin of materials?

What do you know about the role of industry in RM applications and development?

Do you know other professionals suitable for interviewing?

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Chapter 4.

Societal impacts of Regenerative Medicine: reflections on the views of orthopedic professionals.

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Abstract

As the amount of clinical studies in orthopedic Regenerative Medicine (RM) is increasing, it is time to take into account its impact on society. 36 biomedical professionals working at the front row of orthopedic RM were interviewed to explore their attitudes, opinions and expectations regarding the societal impacts of RM. Professionals mainly recognized the societal impacts of *counteraction of ageing*, *prevention of disease*, and *social justice*. The "soft" sides of these impacts were hardly mentioned. Whereas they did not perceive themselves in the position to mitigate these impacts, professionals should take up their role as actor and become involved in the societal debate. This is important as they can co-shape the societal impacts during the developmental process of technologies and thereby stimulate responsible innovation.

Introduction

Our human culture is permeated with technology: we live in a "technological culture" (1). One of the technologies that will impact society is Regenerative Medicine (RM). RM interventions in all types of medical areas are being developed, among which interventions for orthopedic disorders such as disc degeneration and osteoarthritis, cardiovascular disorders (e.g. heart failure) and (degenerative) neurological disorders (2-4). RM is an innovative field of approaches aimed at restoring the original function and structure of tissue, including cell-based interventions, gene transfer and tissue engineering (5). The field distinguishes itself from traditional drugs and surgical procedures due to a combination of characteristics, which include complexity, invasiveness, the aim of regeneration, and the high public and political attention (6;7).

While many of these RM interventions are still in the preclinical phase, it is time to discuss the ethical issues involved in the translational step to clinical research (6-8), also called T1 research, as well as the translation to the public sphere, known as T2 research (9). When considering this step to society, the *hard impacts* can be taken into account, such as the potential safety risks of a technology, cost-effectiveness of an intervention, and the economic value (10;11). However, a new technology can also have *soft impacts*, in the sense that it influences our moral actions, experiences, perceptions, and interactions with others, and as such have an impact on our quality of life (12).

There is an evolving ethical debate about the potential societal impacts of RM, although soft impacts typically receive much less attention than hard impacts (10;13;14). In order to enrich this debate, which mainly takes place in the academic ethics literature, it is useful to incorporate the views of professionals at the forefront of the RM field. This provides insight in whether these stakeholders are aware of the potential impacts of emerging technologies, of which societal impacts they are aware, and how they perceive their role in this debate. This is important as they can co-shape the societal impacts during the developmental process of technologies as they are often close to the development or application of a technique, and thereby stimulate responsible innovation (15). The aim of this study was to explore the attitudes, opinions and expectations of orthopedic biomedical professionals regarding the societal impacts of RM. As our project is embedded in a larger orthopedic RM research project (see below) and as orthopedics is one of the leading fields in RM we focused on professionals working in orthopedics.

Materials and methods

Design

We conducted an empirical, qualitative study to explore the attitudes, opinions, and expectations of orthopedic biomedical professionals regarding the societal impacts of RM. As this was the first study on this topic, we were mainly interested in gaining an impression on 'what' societal impacts the orthopedic professionals discerned, rather than providing explanations for 'why' the individual professionals recognized different impacts. Therefore, we chose for conducting one-to one semi-structured interviews as this allows much room for what the respondents regard important to discuss (via open-end questions) and thereby to generate rich, in-depth understanding of a particular topic (16;17). Inclusion criteria were that the respondent: 1) is in the front row of (pre)clinical orthopedic RM research, and/or 2) is experienced in conducting clinical research or practice in orthopedics. This study was conducted as part of the Dutch BioMedical Materials-funded consortium IDiDAS. IDiDAS involves four academic medical centers, one technical university, and industrial partners and is in the preclinical phase of developing RM interventions for the treatment of intervertebral disc disease. We are embedded in the IDiDAS project as the work package Ethics, in order to identify and evaluate ethical issues in translating RM interventions for orthopedic disorders into patients and society. Since the IDIDAS project is in the front row of orthopedic RM we expected that this network of professionals would correspond with our inclusion criteria. Further, since we are embedded in the IDiDAS project as the work package Ethics it was convenient to use its network. Therefore, our respondents were recruited using the network of this consortium, and by following recommendations from the interviewees (so-called snowball sampling) (18). A topic list, based on existing literature and pilot interviews, was used to guide the interviews but respondents were able to add other aspects (Supplemental File in Chapter 3: Topic List). Both questions about the translation from preclinical research to first-in-human studies (T1 research), and from clinical studies to society (T2 research), were incorporated. In this chapter we report on the attitudes, opinions and expectations regarding the societal impacts of RM by orthopedic biomedical professionals. The results concerning the ethical issues involved in the translation to clinical trials were described in chapter 3(19).

Data collection

In total, 50 people were approached, 10 people did not respond, 4 rejected the invitation and 36 agreed to an interview. Recruitment was ended when saturation was reached, i.e. when no new thematic content was found(20). One-on-one interviews were mainly held with surgeons who were involved in the field of RM or orthopedic research/practice, and with basic scientists not involved in clinical practice but working at the bench (mainly biologists and biomedical engineers) in orthopedic RM (Table 1, page 44-45).

The interviews were conducted by SN between April 2012 and November 2012. The interviews lasted between 30 and 75 minutes and most interviews took place at the workplace of the respondent. Five interviews were done by telephone.

Analysis of results

The interviews were audiotaped, transcribed verbatim, and stored anonymously, after permission was given by respondents. Data analysis was based on the constant comparative method, which involves going back and forth from the data to develop codes, concepts and themes (21). SN independently coded the full transcripts by labeling units of texts that referred to one or more topics relevant to the study purpose. Coding was done with NVivo 8 software (22). Two members of the research team - TT and AB - read the full transcripts with coding and checked the codes for consistency. The codes were adjusted by comparison across transcripts and by discussion with the other authors. After consensus on coding was reached the codes were developed into higher order concepts and themes to provide a framework for coding subsequent transcripts. Subsequently, the themes for discussion were discussed with the whole research team. We do not show which percentage or amount of respondents expressed a certain opinion, as quantification does not correspond with the aim and method of our study(17).

Results

Three main themes of societal impacts emerged from the data: 1) counteraction of ageing, 2) prevention, and 3) social justice.

Theme 1: RM and counteraction of ageing

Several professionals brought up that RM might affect our perception of old age. The respondents suggested that some signs and symptoms of musculoskeletal disorders – like disc degeneration, osteoporosis and osteoarthritis- 'naturally' occur in the process of ageing. As the ultimate goal of RM is to treat and prevent degeneration, RM could in a certain way counteract ageing. However, mainly surgeons suggested that ageing and the corresponding process of degeneration should not be perceived as a disease but as a normal process of life.

"The question is whether disc degeneration is a disease. In the clinic I explain to my patients that we all grow older, luckily, and during this process of ageing grey hair and wrinkles appear. Wrinkles develop because water recedes from your skin. The same thing occurs all over your body, including your discs. This is visible on MRI: the water content is decreasing. That's nothing serious, as it is just the process of normal ageing." (orthopedic surgeon)

Hence, they doubted whether it is appropriate to start with a RM intervention, when this is aimed at discomforts occurring due to old age. Concerns were also raised over what would be the advantage of RM to treat degeneration of a specific tissue while other tissues in the body continue degenerating.
On the other hand, both surgeons and scientists pointed out that it is the duty of physicians to help patients with complaints, even though these might be related to ageing. And although, for example, disc degeneration itself is a 'normal' process, it can lead to serious pathology that should be treated, like stenosis, herniated discs, and scoliosis. Furthermore, some also state that pain in the end stage of life should be prevented as much as possible.

"We do not want to become older, with the foresight that after the age of 70 we are sitting around, waiting to die. We want to stay active in social life and society. [..] At a certain moment our life is finished, and we should accept that, but we should ensure a high quality of life. I think we should treat these types of issues." (basic scientist)

While the use of RM for orthopedic disorders is unlikely to extend natural life span and suppress the process of ageing, there were some respondents, both surgeons and basic scientists, who worried about this when they considered the use of RM for cardiovascular disorders. The respondents point out various reasons why life extension through RM interventions would be morally problematic. Some seem to be motivated by doubts whether it will contribute to a higher quality of life. Others opposed life extension by pointing out both the high long-term costs of such RM interventions as well as unnaturalness. One of the basic scientists who adhered to this last position argued that mankind's lifespan is largely predetermined by our genetic makeup and that it was not up to him as a scientist to change this. Slightly increasing human lifespan would be permissible, but RM should not be aimed at achieving eternal life.

"You will have to accept certain discomforts in your life, instead of thinking that we can solve everything and you can become a 100-year old while your body does not grow older than twenty." (orthopedic surgeon)

Theme 2: Prevention of disease due to RM

Another important theme the respondents raised was the use of RM for preventive goals.
The main issue that arose was whether RM should be used for treatment and secondary prevention (preventing progression of disease), or whether it could also be used for primary prevention (preventing the occurrence of disease).

"Are we going to treat everyone? Are we going to improve everyone so that they will not show any signs of wearing and tearing? Or are we only going to treat those who already have symptoms? Maybe you are too late when patients already have symptoms." (orthopedic surgeon)

Many respondents regarded it appropriate to use RM for prevention purposes as long as there were certain signs and symptoms of disease. Especially the surgeons were concerned that persons would be regarded sick while not feeling ill, contributing to medicalization in society. Others worried that this primary prevention could evolve into interventions which improve human functioning beyond what is necessary to sustain good health, also called 'enhancement'(23). Another group of respondents were afraid that people might become reluctant to use regular methods of prevention, like upholding a healthy lifestyle, when, for example, an injection with stem cells could relieve symptoms as well. Additionally, some doubted the long term beneficial effects of prevention by means of RM especially since for the prevention of degeneration one intervention for the following 30 or 40 years will not be sufficient, but instead regular scans, checks, and invasive insertions might be required. On the one hand, some surgeons doubted whether novel technologies would be more cost-effective than preventing symptoms by changing lifestyle habits for example. On the other hand, others stated that primary prevention could be beneficial for the individual patient, and could have positive impacts on society by preventing large amount of health care costs for the late stage consequences. A basic scientist mentioned that the ultimate aim should be to get rid of prostheses as these are not the same as a person's own joint, while many surgeons noted that hip and knee prostheses are treatments with the highest patient satisfaction rates.

Theme 3: Social justice and RM

The professionals, mainly the surgeons, wondered what influence the introduction of RM techniques in daily clinical practice could have on our views on justice, and how potential inequity resulting from expensive RM interventions can be mitigated. Introducing RM in orthopedics is perceived to be a costly project for which neither government nor healthcare insurers are likely to reimburse for each individual patient.
Some posed an economic libertarian position towards this problem, as they consider it possible that RM techniques are made available to the public through private clinics. While this might result in the worsening of existing inequalities, these professionals do not consider this to be problematic. They argue that differences in income and wealth are inherent to our society and that people with sufficient money to undergo RM interventions, should not be hindered.

"This will lead to a division in healthcare. Is that a problem? No, it is not, since this division already exists. Not everyone sleeps in an expensive hotel and nobody complaints about that. You should provide people the opportunity to climb up and help the lesser-off in society, but should all those people drive a Ferrari?" (orthopedic surgeon)

Another group of professionals holds a social liberal position and searches for ways to prevent these injustices when translating RM into society. Allowing the wealthy to access RM

interventions without granting the same to the lesser-off in society, will enhance the division in access to health care. As a result the rich would become healthier and live longer, while the poor will only remain eligible for regular care. Such unequal access to RM interventions could further increase the social inequalities that are already present in society.

"The current existing injustices might get worse, since there is already a considerable difference in the health and life expectancy between people with a high economic status compared with those of lower economic status. So the people with the money and the brains, they will be able to enhance their bodies, allowing them to live longer and healthier. […]. This will lead to a biological caste system." (orthopedic surgeon)

Apart from this argument, some respondents thought RM interventions might be useful, but too expensive to develop. They deemed it hard to justify investing large amounts of money in RM in the light of other needs of society. The money could be better spent on improving regular treatments in national healthcare or be transferred to other countries where the quality of health care is lower. They seem to state that if you have a large amount of money it would be more just to distribute this to a large group of people, rather than to provide a select few with RM based therapies.

Discussion

Three types of reflections on the results of this empirical research can be made regarding 1) the type of impacts discerned, 2) the content of the themes, and 3) the role perception of the professionals.

First, an important finding from this qualitative research is that professionals were aware that RM technology will have societal impacts, but that they mainly discern the hard sides of these impacts, such as (quantifiable) cost/risk-benefit considerations, rather than the soft impacts. Some also mentioned soft impacts, for example when a preventive injection could lead to giving up a healthy life style or the increase in social inequalities. Since soft impacts are harder to quantify, and thereby more difficult to grasp, this could explain why these impacts were mentioned less.

Second, the three main themes that were mentioned in the interviews also return in debates on other types of emerging medical technologies and therefore no novel themes appeared. However, what the responses made us aware of is that RM technologies add a new dimension to these existing debates. For example, since the last half of the twentieth century, the interest and possibility of developing anti-ageing products has increased, via the use of 'simple' interventions like dietary or hormone supplements, lifestyle changes, or cosmetic interventions to high-tech interventions, like hip prostheses (24). For all anti-ageing products the same ethical tension is applicable: whether we should accept that we age as

part of life, or whether we should intervene in the ageing process as it is abnormal (25). What is new for RM technologies is that for degenerative disorders it might become possible to intervene in a quite early stage in ageing, and thereby postpone ageing up to a certain extent (26;27). This is a further-reaching form of anti-ageing than slowing ageing as many other anti-ageing products do. If RM will be applied in other fields than orthopedics, for example RM for cardiovascular disorders, RM might also be able to extend the human life span, raising other moral issues as well. Also the (negative) consequences of prevention is currently highly discussed due to the development of vaccines, screening technologies and genetic tests, among other (28). As such, this societal impact is similar to other fields, but what makes RM interventions particularly challenging are the extensive degree of prevention they could encounter and their invasive character. With regard to social justice it is argued that the introduction of RM could increase the division of health between the rich and the poor, as only a small part of society being able to afford RM technologies. These considerations account for many interventions as is also seen in medical tourism for currently existing and novel expensive technologies, such as cardiac by-passes or organ transplantation (29). However, as RM interventions could reverse or prevent degeneration of several bodily tissues the potential impact on the health status of individuals might be high, and, if not equally distributed, potentially leading to larger gaps in health status.

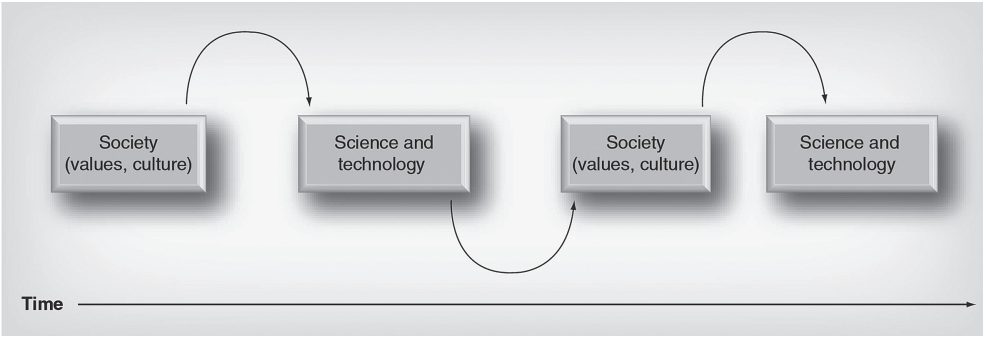
This shows how RM fits within the contemporary debate on the question to what extent we want to afford interventions that aim to prevent ageing, but also brings new considerations into current debates.

The third element of this reflection concerns the role of professionals in the debate about societal impacts. We observed that respondents who were closer to clinical practice, i.e. the surgeons, generally identified more societal impacts. This is not surprising as clinicians are directly involved in patient care and therefore have a view on the characteristics and demands of patients, and are potentially more aware of general issues in health care. However, the surgeons appeared not to perceive themselves as actors in this debate, as hardly any remarks are made on whether they can become co-responsible for these societal impacts in a certain way, apart from some hard impacts like minimizing the risks, and maximizing efficacy. For instance, none of the professionals discuss how they can be involved in 'shaping' the technique to avoid that it can lead to patients giving up a healthy lifestyle, or how to prevent social injustices, for example by using less expensive materials. They seem to have a so-called neutral view on technology that assumes technology is objective and value-free(30). It appears that they regard the users of the technology, and the policy makers that decide to implement these, responsible for the effects on human life (31). This corresponds with the results of a project with a related topic in which it appeared that tissue engineers hardly reflected on and took responsibility of the societal impacts of the technology they are developing (32).

According to the interactionist, also called constructivist, perspective on technology and society, the values of developers and applicants of technology shape the design of a

technology and hence influence society. Science (including the clinicians that will apply these) and technology are not autonomous realms that operate independent of society, but they are mutually constitutive: they are all actors that continuously affect each other in the development of science and technology (33)(Figure 1). Hence, surgeons, and clinicians in general, could be valuable in transferring their views on societal impacts to the scientists who are actively involved in developing the technology. At the same time, in order to ensure mutual understanding, these clinicians can translate the knowledge from the laboratory practice to the public at large (31).

Figure 1: Interactionist perspective on the development of science, technology and society



This interactionist perspective can also illustrate the rise of RM, as RM fits in a society where the liberal ideology has gained increased importance. In liberalism concepts such as autonomy and personal freedom are central values, and especially these values are threatened by disease of old age. Degeneration could lead to a decreased mobility and greater dependency on others, limiting individual freedom(34). This may have formed an impetus, be it conscious or unconscious, to start developing RM technologies.

Strengths

The strength of this empirical study is that it provides a first insight in to what extent professionals in the front row of RM recognise societal impacts of RM techniques and how they perceive their role in mitigating these. In addition, the semi-structured interviews allowed much more room for the respondents' views than, for example, a questionnaire would have had. Due to the large number of respondents it is highly likely that among these stakeholders no potential impacts were missed and that a rich impression has been provided of the attitudes, opinions, and expectations within this group. Furthermore, although most respondents were involved in the orthopedic field, the study results and discussion are also

relevant and inspiring for other RM fields, mainly since also other academics ethics literature on these themes are not specific for orthopedic RM.

Limitations

A limitation of this research is that mainly male, Dutch and British (i.e. Western) respondents were included, while respondents with a different national, cultural or religious background (both within Europe and on other continents) and females could show different or additional opinions and/or expectations. This would have allowed an even broader view on the societal impacts. For example, certain studies have shown that males are more risk-tolerant and therefore also more supportive on new technology in general(35) This lack of variation in nationality was caused by the fact that the respondents were recruited via the IDiDAS consortium which only contains Dutch partners. The relative lack of females is probably due to the minority in female professionals in the field of orthopedic surgery which reduced the chance we got into contact with them.

Conclusions

An important finding from this empirical research is that these actors are aware of the societal impacts of a novel technology like RM, although they mainly seemed to be aware of the hard impacts in terms of risks and benefits. The discerned societal impacts in terms of ageing, prevention and social justice itself have recurred in other debates about emerging technologies, but RM brings new considerations into these debates. Furthermore, it appeared that the clinicians were highly reflexive but also felt not involved in the debate, although they are the ones in between the scientists in the laboratories developing RM technology and society.

Future perspective

As science, society and technology are mutually constitutive we have argued that clinicians should become more involved in the societal debate. During the development of RM technology they should inform scientists, which appear less aware of societal impacts, probably due to their different working environment. Furthermore, in the education of scientists and engineers more awareness and reflectiveness could be raised of the impact their future work has on society, regarding other impacts than just economic or health benefit consequences. By taking up their roles as actor, scientists and clinicians can co-shape the societal impacts and drive responsible innovation in RM. Via this way RM

interventions are more likely to be successfully received by society. To gain more insight on this topic, incorporating the views of a wider variety of stakeholders, from different sectors (specialisations, patients and funders) and background, is essential to allow further insight.

Executive summary

The societal impacts which professionals discern

Professionals recognise a part of the same societal impacts of RM as have been discussed so far in academic ethics literature

Three main domains of societal impacts were mentioned by the professionals: counteraction of ageing, prevention of disease, and social justice

Mainly the hard sides of impacts were discerned, such as cost/risk-benefit considerations, rather than the soft impacts, i.e. influence on perception and experience

The perceived role of professionals

Professionals appeared not to perceive themselves as actors in the societal debate, as hardly any remarks are made on how they can become co-responsible for these societal impacts

What we learn from professionals

The three main themes that were mentioned in the interviews also return in debates on other emerging medical technologies, but RM brings in new considerations

Novel is that RM technologies could probably intervene in a quite early stage in ageing, and thereby could postpone ageing up to a certain extent

Furthermore, what makes RM interventions particularly challenging is the extensive degree of prevention they could encounter and the invasive manner of prevention

RM could have a large influence on the gap in health status between rich and poor (social injustice), as it could reverse or prevent degeneration of several bodily tissues

What professionals can learn

By taking up their roles as actor, scientists and clinicians can co-shape the societal impacts and drive responsible innovation in RM

Clinicians could be valuable in transferring their views on societal impacts to the scientists who are actively involved in developing the technology

At the same time, in order to ensure mutual understanding, these clinicians can translate the knowledge from the laboratory practice to the public at large

Via this way, RM interventions are more likely to be successfully received by society

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Chapter 5.

Stem cell trials for cardiovascular medicine: ethical rationale

Tissue Engineering Part A. 2014;20(19-20):2567-74

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Abstract

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 adult 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 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, and 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 improved 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 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 create 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 non evidence-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.

Table 1. Ethical challenges and considerations in stem cell randomized controlled trials for cardiovascular medicine

Ethical challenge	*Points to consider*
Risk-benefit assessment	Be aware of the uncertainty of risks and benefits; this depends on type of stem cells, previous evidence and experience with reference classes Be aware that there are physical risks due to invasiveness of the intervention, and psychological burdens due to randomization Make sure to manage and, if possible, minimize risks 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 Make sure to maximize benefits, including knowledge value about working mechanism
Choice for outcome measures	Be aware that clinical improvement as outcome measure is important, but consider whether this fully captures patient's perspective Be aware that clinical improvement is affected by placebo effects and other nonspecific effects and consider to elude this by blinding Consider to incorporate outcome measures that assesses (directly or indirectly) regeneration to increase information about working mechanism (if a reliable test is available) Be aware that regeneration might not correlate with clinical outcome
Choice for comparator	Consider whether there is a treatment in clinical practice that provides net medical advantage, which should not be withheld to the comparator group Consider whether sham is methodologically necessary, among others, depending on type of outcome measure, and chance of placebo effects If sham is desirable, consider whether physical and psychological risks are proportionate to expected benefits to science and society
Participant selection	Consider which participant group is most appropriate. This depends, among others, on the aim of the study, and the toxicity of the intervention Be aware that in end-stage participants: – 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	Be aware that the risk of therapeutic misconception may be increased due to use of invasive intervention, and high expectations Be aware that the chance of therapeutic misconception is higher if sham as comparator is used, and if no option participants are included Next to therapeutic misconception, be also aware of therapeutic misestimation of benefits and risks Enhance informed consent procedure, both through the manner and content of information

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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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Chapter 6.

Placebo in autologous cell-based Interventions hard pill to swallow?

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Cell-based strategies are under intense investigation in the pursuit to develop new effective treatment protocols for ischemic heart disease (IHD). These strategies have been mainly based on the use of tissue-specific autologous stem/progenitor cells such as cells from bone marrow, adipose tissue, or the heart itself (1). Several of these cell types have reached the phase of clinical testing (2;3). Clinical trials, in particular trials investigating cell-based interventions, entail inherent scientific and ethical challenges. Due to the combination of the relative lack of experience with cell-based interventions, the complexity, the variability (especially when autologous cells are used), and the invasive character, traditional ethical issues get a new perspective. One of these issues is the choice for the comparator (4).

Treatment effect is generally assessed in clinical trials by means of superiority of the novel intervention over standard clinical care or placebo. Placebo is used to conceal intervention allocation both for the patient and investigator-physician (5). In pharmaceutical clinical trials, the placebo is often a capsule or tablet indistinguishable from the investigational new drug. However, in clinical trials assessing autologous cell interventions for heart disease, proper blinding can only be achieved when participants allocated to the placebo group undergo the identical harvesting procedure (e.g., bone marrow aspiration in the case of bone marrow mononuclear cells) as well as a sham delivery procedure to the heart undistinguishable from the cell delivery procedure. If the interventional cardiologist is not involved in the follow-up and/or outcome analysis, the sham procedure may not necessitate an actual injection with a placebo solution identical to the cell suspension. Either way, in contrast to placebo tablets, autologous cell interventions expose the control group to risk and harm, raising ethical concerns.

To date, little is known about the extent to which sham interventions in cell-based trials are performed. To address this question, we conducted a systematic review on published reports of randomized clinical trials (RCTs) investigating efficacy of autologous cell interventions in patients with IHD. We assessed how RCTs were designed regarding cell harvesting and/or cardiac sham delivery, whether this depended on the type and stage of cardiac disease, and the adverse events rate in sham procedure patients. A search syntax was developed based on relevant synonyms for domain, which is patients with IHD, and determinant, which is cell intervention delivered to the heart (i.e., intracoronary, intramyocardial, epicardial injection, and retrograde venous injection) (see Supplemental File, Search syntax). The outcome - efficacy of cell intervention - was deliberately withheld from our search syntax to avoid potential reporting and retrieval bias. A systematic literature search was conducted in MEDLINE and EMBASE on the 13th of May 2013. Two reviewers (S.K., J.W.) independently screened title and abstract of studies in accordance of in-/exclusion criteria (see Supplemental File, Figure 1). The selected articles were crosschecked to identify relevant studies missed by the initial search using ISI Web of Science.

A total of 56 RCTs were identified that were published between 2001 and 2013 (see Supplemental File, Table 1). In total 3,610 patients were included in these studies, of which 2,189 (61%) received autologous cells, compared to 1,421 (39%) controls. In 75% of

studies, bone marrow mononuclear cells were the investigational cell type. Diagnosis was acute myocardial infarction (MI) in 2,463 patients (982 controls [40%]), compared to 1,147 patients (439 controls [38%]) with chronic IHD (i.e., refractory angina or post-MI heart failure). Combined cell harvesting and sham cardiac delivery, thereby ensuring patient and investigator blinding, was performed in 22 of the 56 studies (39%). Analysis divided for IHD type revealed that 11 of 36 studies (31%) used sham delivery in acute MI and 11 of 20 studies (55%) in chronic IHD (chi-square; p ¼ 0.09). Apparently, use of placebo is generally not preferred in the acute setting of MI in contrast with an elective cell intervention procedure for chronic IHD. Furthermore, in 1 study, participants allocated to the control group underwent cell harvesting but no sham cardiac injections, while the rest of the studies used usual care as a comparator.

Out of 22 studies that used placebo, adverse events in controls were reported in 5 studies (23%), all of which investigating bone marrow cells. A combined endpoint analysis of major cardiovascular events revealed that intracoronary infusion of a placebo solution did not lead to heightened mortality or serious morbidity in these 5 studies. With regard to the cell harvesting procedure no adverse events were reported.

Three major conclusions emanate from our study: 1) 39% of RCTs investigating efficacy of autologous cell intervention used a double-blind trial design based on a sham procedure; 2) trials using sham delivery were less frequently observed in acute MI compared to chronic IHD; and 3) 23% of these trials reported data on (minor) adverse events. This report shows that the choice for the control group for cell-based interventions in cardiology differs among research groups, which could be related to diverging views on scientific necessity and ethical acceptability of sham. The diversity in the choice of the comparator group, shown by this empirical report, supports the need to clarify when and under what conditions sham is scientifically necessary and ethically acceptable, and when another comparator is more appropriate in clinical trials investigating cell-based interventions for cardiology and other medical fields. This will, among others, probably correlate with the study population, and the risk profile of the sham procedure. Hence, this report can function as a starting point to formulate guidelines for researchers that aim to set up a cell-based randomized trial.

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Supplemental File

Search Syntax

Search syntax Medline

#1: heart[Title/Abstract] OR cardia*[Title/Abstract] OR myocardia*[Title/Abstract] OR coronary*[Title/Abstract] OR cardiomyopath*[Title/Abstract]
#2: failure[Title/Abstract] OR decompensation[Title/Abstract] OR infarction[Title/Abstract] OR
ischemi*[Title/Abstract] OR ischaemi*[Title/Abstract] OR disease[Title/Abstract] OR dysfunction[Title/Abstract] OR disfunction[Title/Abstract] OR angina[Title/Abstract]
#3: stem*[Title/Abstract] OR progenitor*[Title/Abstract] OR (bone[Title/Abstract] AND marrow*[Title/Abstract]) OR precursor*[Title/Abstract]
#4: cell*[Title/Abstract]
#5: myoblast*[Title/Abstract]
#6: transcoronar*[Title/Abstract] OR intracoronar*[Title/Abstract] OR transendocardial*[Title/Abstract]
OR intramyocardial*[Title/Abstract] OR intravenous*[Title/Abstract] OR transvenous[Title/Abstract]
Search: #1 AND #2 AND ((#3 AND #4) OR (#5)) AND #6

Search syntax Embase

#1: heart:ti,ab OR cardia*:ti,ab OR myocardia*:ti,ab OR coronary*:ti,ab OR cardiomyopath*:ti,ab
#2: failure:ti,ab OR decompensation:ti,ab OR infarction:ti,ab OR ischemi*:ti,ab OR ischaemi*:ti,ab OR
disease:ti,ab OR dysfunction:ti,ab OR angina:ti,ab
#3: stem*:ti,ab OR progenitor*:ti,ab OR (bone:ti,ab AND marrow*:ti,ab) OR cardia*:ti,ab OR precursor*:ti,ab
#4: cell*:ti,ab
#5: myoblast*:ti,ab
#6: transcoronar*:ti,ab OR intracoronar*:ti,ab OR transendocardial*:ti,ab OR intramyocardial*:ti,ab OR
intravenous*:ti,ab OR transvenous:ti,ab
Search: #1 AND #2 AND ((#3 AND #4) OR (#5)) AND #6

Figure 1. Flowchart of the systematic search conducted on 13th of May, 2013 on Medline and Embase. IHD denotes ischemic heart disease, AMI; acute myocardial infarction, CHD; chronic ischemic heart disease.

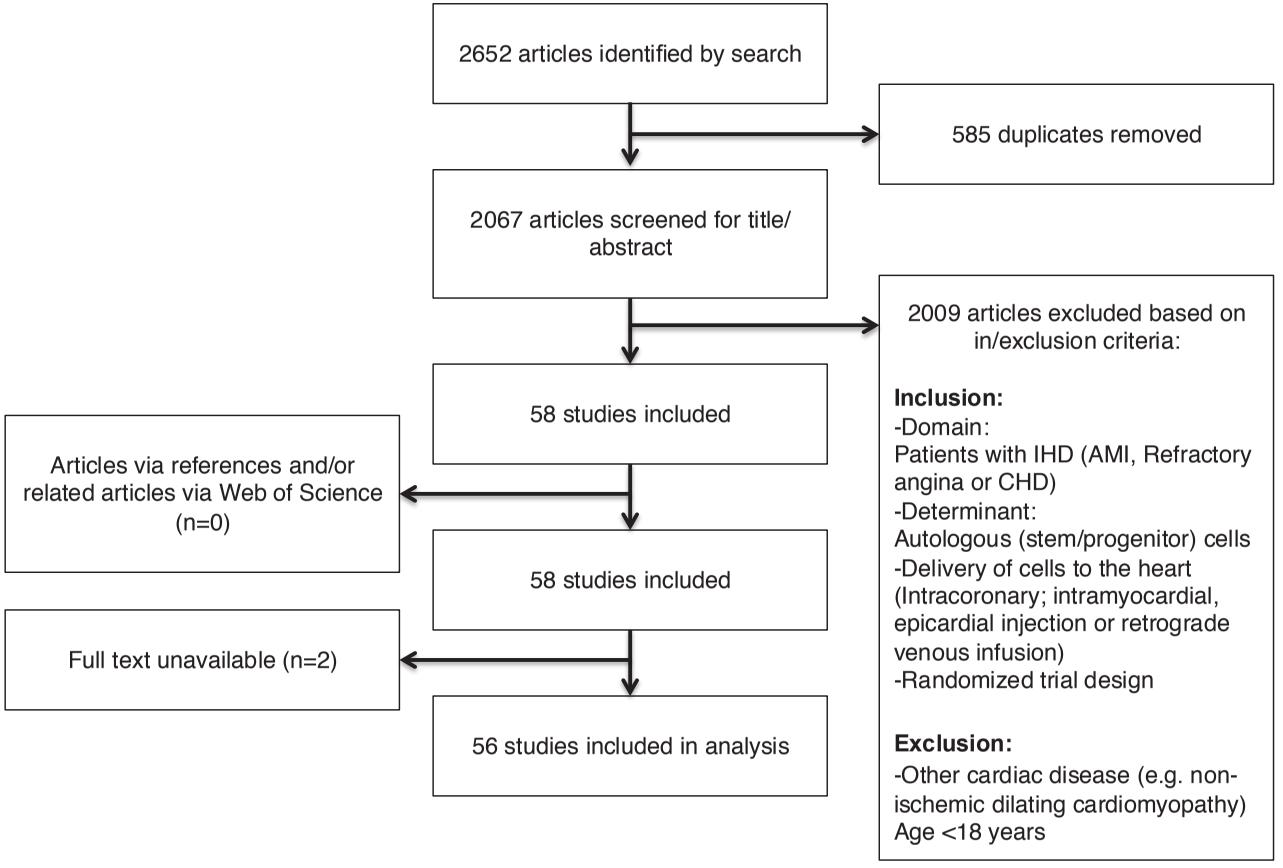

Table 1. Characteristics of studies included in the analysis

Source	Year	Sample size	Type of IHD	Cell type	Route of Delivery	Cell harvesting in controls	Sham delivery procedure
Ang et al(1)	2008	63	CHD	BMNC	IC	BM	No
Assmus et al(2)	2006	92	CHD	BMNC	IC	None	No
Assmus et al(3)	2013	103	CHD	BMNC	IC	BM	Yes
Bolli et al(4)	2011	23	CHD	CSC	IC	None	No
Cao et al(5)	2009	86	AMI	BMNC	IC	BM	Yes
Chen et al(6)	2004	69	AMI	MSC	IC	BM	Yes
Colombo et al(7)	2011	10	AMI	CD133+ cells	IC	None	No
Dohmann et al(8)	2005	21	CHD	BMCN	IM	None	No
Erbs et al(9)	2005	26	CHD	BCPC	IC	Venous blood	Yes
Ge et al(10)	2006	20	AMI	BMNC	IC	BM	Yes
Grajek et al(11)	2006	45	AMI	BMNC	IC	None	No
He et al(12)	2010	41	CHD	BMNC	IC	None	No
Hendrikx et al(13)	2006	20	CHD	BMNC	EI	BM	Yes
Herbots et al(14)	2009	67	AMI	BMNC	IC	BM	Yes
Hirsch et al(15)	2010	200	AMI	BMNC/BCPC	IC	None	No
Huikuri et al(16)	2008	80	AMI	BMNC	IC	BM	Yes
Janssens et al(17)	2006	67	AMI	BMNC	IC	BM	Yes
Kang et al(18)	2004	27	AMI	BCPC	IC	None	No
Karpov et al(19)	2005	44	AMI	BMNC	IC	None	No
Lipiec et al(20)	2009	39	AMI	BMNC	IC	None	No
Lunde et al(21)	2005	49	AMI	BMNC	IC	None	No
Lunde et al(22)	2006	100	AMI	BMNC	IC	None	No
Makkar et al(23)	2012	25	AMI	CSC	IC	None	No
Malagoli et al(24)	2010	41	AMI	BMNC	IC	None	No
Meluzin et al(25)	2006	66	AMI	BMNC	IC	None	No
Menasche et al(26)	2008	97	CHD	SM	EI	Surgical biopsy	Yes
Miettinen et al(27)	2010	78	AMI	BMNC	IC	BM	Yes
Nasseri et al(28)	2013	77	AMI	CD133+ cells	IM	None	No
Noguiera et al(29)	2009	30	AMI	BMNC	IC	None	No
Penicka et al(30)	2007	27	AMI	BMNC	IC	None	No
Perin et al(31)	2011	30	CHD	BMNC	IM	BM	Yes
Perin et al(32)	2012	20	CHD	BMNC	IM	BM	Yes
Perin et al(33)	2012	92	CHD	BMNC	IM	BM	Yes
Perin et al(34)	2003	21	CHD	BMNC	IM	None	No
Piepoli et al(35)	2010	38	AMI	BMNC	IC	None	No
Plewka et al(36)	2009	60	AMI	BMNC	IC	None	No
Pokushalov et al(37)	2009	99	CHD	BMNC	IM	None	No
Pokushalov et al(38)	2010	109	CHD	BMNC	IM	None	No
Povsic et al(39)	2011	20	CHD	SM	IM	Surgical biopsy	Yes
Quyyumi et al(40)	2009	31	AMI	CD34+ cells	IC	None	No

Source	Year	Sample size	Type of IHD	Cell type	Route of Delivery	Cell harvesting in controls	Sham delivery procedure
van Ramshorst et al(41)	2009	50	CHD	BMNC	IM	BM	Yes
Sanchez Fernandez et al(42)	2012	120	AMI	BMNC	IC	None	No
Schächinger et al(43)	2006	204	AMI	BMNC	IC	BM	Yes
Shihong et al(44)	2012	112	CHD	CD34+ cells	IC	BM	Yes
Silva et al(45)	2009	30	AMI	BMNC	IC	None	No
Tendera et al(46)	2009	200	AMI	BMNC	IC	None	No
Terrovitis et al(47)	2011	22	AMI	CD34+cells	IC	None	No
Traverse et al(48)	2011	87	AMI	BMNC	IC	BM	Yes
Traverse et al(49)	2012	120	AMI	BMNC	IC	BM	Yes
Trzos et al(50)	2009	62	AMI	BMNC	IC	None	No
Tse et al(51)	2007	28	CHD	BMNC	IM	BM	Yes
Wohrle et al(52)	2010	42	AMI	BMNC	IC	BM	Yes
Wollert et al(53)	2004	60	AMI	BMNC	IC	None	No
Xu et al(54)	2009	80	CHD	BMNC	IC	None	No
Zhan-quan et al(55)	2007	70	AMI	BCDC	IC	None	No
Zhang et al(56)	2007	70	AMI	CD34+ cells	IC	None	No

CHD denotes chronic ischemic heart disease; AMI denotes acute myocardial infarction; BMNC denotes bone marrow mononuclear cell; BCPC denotes blood-derived circulating progenitor cell; SM denotes skeletal myoblast; BM denotes bone marrow aspiration

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Chapter 7.

Reconsidering the ethics of sham interventions in an era of emerging technologies

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Abstract

Background Our aim was to ethically evaluate the arguments in favor and against sham interventions, as presented in literature. Two developments underscore the need to reconsider the ethics of sham interventions. First, the number of clinical trials investigating interventions in the field of Regenerative Medicine (RM) are increasing, in which the choice for a placebo requires an invasive placebo. Second, the increased awareness of the lack of systematic research in surgery stresses the need to discuss the necessity and acceptability of sham-controlled clinical trials.

Methods A systematic search in Medline was performed, of which 104 articles were considered relevant.

Results Arguments in favor of a sham controlled design are that it increases the scientific validity and the benefits to society while at the same time the risks and harm can be acceptable. Arguments against sham controls include that they pose unacceptable risks to participants, present difficulties with informed consent, that the use of deceptive tactics is unethical, and that the feasibility of such controls is compromised due to a lack of public support.

Conclusions None of the published literature fully rejects sham interventions, and many regard sham interventions acceptable provided the conditions of scientific necessity, reasonable risks, and valid informed consent are fulfilled. Further debate should no longer address *whether* a sham control is ethically acceptable, but rather *when* these conditions are fulfilled.

Introduction

An important ethical challenge in the design of clinical trials is the decision whether a control group is necessary and if so whether this control group should receive placebo, standard of care, or no intervention. A placebo group can allow blinding of participants and investigators. Placebos for other types of procedures than pills are called sham interventions, which can range from (minimal) invasive surgical procedures to other interventions like radiotherapy (1;2). This chapter concentrates on the ethics of invasive sham procedures, also known as placebo surgery: i.e., procedures that are characterized by a physical change of bodily tissue through manual or robotic operation and thereby inherently imply physical harm and/or risks.

A range of invasive sham interventions have been used in clinical trials, examples include investigating the efficacy of arthroscopy (3), vertebroplasty (4;5), subcutaneous placed stimulators(6), open operative neurectomy in the abdominal wall(7), intracoronary infusions with a cell intervention(8), intravitreal injections (9), and, recently, meniscectomy (10). The debate about the ethics of sham interventions emerged more than 10 years ago in response to two, fetal stem cells trials for Parkinson's disease (11;12). These trials evoked debate due to the high risks to the control group, because the control group underwent drill holes without the introduction of stem cells.

Two developments in contemporary medicine underscore the need to reconsider the ethics of sham interventions. First, more and more clinical trials investigating innovative approaches in Regenerative Medicine (RM) are being proposed and conducted, including randomized controlled trials (RCTs) with a sham intervention as a control group (13-15). Such research studies in RM encompass (stem) cell-based interventions, gene transfer, use of biomaterials, or a combination of these, often aimed at reversal of organ failure and degenerative disorders (16). Insertion of these novel interventions is performed via surgery or injection(s) in the (systemic) circulation, target tissue or organ (15;17).

Second, increasing attention is being paid to the negative consequences of poor quality or even lack of clinical research for surgical procedures (18-21), leading to a lack of evidence-based practice in several fields of surgery (22). This awareness is fuelled by clinical trials, such as the use of a certain bone cement for vertebroplasties, that appear to have been researched insufficiently and led to unnecessary harm and even death to patients and public concern (23). Because an RCT is often assumed to provide the highest level of evidence in surgery, it is expected that the need of conducting double-blinded trials will also increase, although an RCT is not appropriate for all types of interventions (24;25). As currently neither the FDA nor the EMA provides clear guidance on when the use of sham interventions is acceptable, it is important to reflect on the scholarly literature. Our work aims to ethically evaluate the key arguments in favor and against sham procedures as they appear in the literature. We will end with suggestions about how to move the debate forward.

Methods

On July 21, 2014, a search in the electronic database of Medline was performed using the key words “ethically,” “ethical,” “ethics”, “morality”, “moral”, and “morally” in combination with the key words “placebo surgery”, “placebo intervention”, “surgical placebo”, “sham surgery”, “sham intervention”, “sham procedure”, “sham”, and “sham-controlled”. The inclusion and exclusion criteria were defined prior to the literature search by discussion among all authors. S.N. screened the title and abstract of studies in accordance with our inclusion and exclusion criteria. The selected articles were crosschecked to identify relevant studies missed by the initial search. In total, 104 articles were included (Figure 1). S.N. collected the provided arguments in the papers and recorded them in an argumentative scheme. After that, the type of arguments were clustered in sets and separated in arguments in favor and against sham controls. Some (review) articles referred to arguments put forward in other work; in this chapter, only the original article is referred to.

Arguments in favor of acceptability of sham controls

Sham increases scientific validity

The first argument to include a sham procedure is that it increases the scientific validity of an RCT (2;26-28). A comparison of the experimental intervention with a sham intervention allows to blind the patient and/or investigator and thereby, discern between specific effects of the intervention and other, non-specific effects such as reporting bias, and performance bias (e.g., difference in care based on the allocated arm) (2;28;28-31). Furthermore, a blinded study prevents the lack of adherence to the allocated arm (32). Including a placebo in surgical trials is considered to be especially important, because placebo effects and distorted participant reporting appear to be greater in surgical trials than in pharmacological trials (27;28;30;33-39). Factors such as need for hospitalization, the involved rituals in surgery, pain management, ancillary treatment, greater stress, and the disease recognition that surgical patients receive, can heighten placebo effects (34;35;40;41). Correcting for and even recognizing placebo effects becomes more important as surgery is moving toward an increased use of subjective (or soft) outcome measures such as quality of life which are prone to be influenced by placebo effects (38;39;42-44). In contrast, in the past surgical procedures were mainly life-saving operations, in which the response to an intervention is more dramatic and thereby, less likely to be biased(38).

A sham control increases benefits to future patients and society

A second argument in favor of sham-controlled clinical trials is the increased likelihood of benefits to future patients and society, because inclusion of a sham group leads to knowledge

that will prevent the introduction of insufficiently proven, potentially risky interventions in clinical practice (2;35;38;45) and thereby, prevent unnecessary and often expensive costs to the health care system (2;13;28). Numerous examples of surgical interventions exist that have been applied in clinical practice, but only later have appeared to be ineffective after the conduct of sham-controlled studies (27;28;38;44;46-49). Because invasive interventions are costly and may potentially cause harm, this argument provides reasons to ensure that such interventions are tested with rigorous scientific scrutiny (38;48).

Risks and harms of a sham control can be acceptable

A third argument for using sham interventions is that the risks and harms to the research participant in the sham group can be considered acceptable. A sham intervention involves inherent risks and harms due to its invasiveness, in contrast to placebo pills. Different conditions are put forward under which the risks of sham interventions are acceptable.

The predominant line of reasoning in much of the literature is that the risks and harms are acceptable when a favorable risk-benefit balance is achieved. Because it is argued that a sham intervention cannot provide individual benefits to participants, the risks and harm of a sham control to the study participants need to be weighed with the potential benefits of the trial to science and society (38;44;50-53). Analogy is drawn between sham interventions and other interventions in research that are not compensated by potential individual benefit, but are justified by the expected benefits for science and society (2;28;33;34;38;44;54). Examples are diagnostic studies (e.g. muscle biopsies, bronchoscopies), studies involving healthy volunteers, phase I studies, or studies aimed at understanding pathophysiology (2). Some authors argue that in the risk-benefit ratio also the individual benefits due to the placebo effects of the sham intervention should also be included (1;27;38;55-59).

Second, some maintain that an additional requirement to the first condition should be that the risks must be minimized. Risk minimization means that measures are taken to decrease the inherent risks for the sham group, for example by using a less risky anesthetic or using only superficial, less invasive approaches, while at the same time ensuring a valid research design (28;41;60). Furthermore, some state that when no alternative design is suitable to acquire reliable and valid evidence ánd poses less risks, the risks are minimized (2;28;34).

An additional condition that a few authors mention is that the risks of the sham intervention arm should not exceed a risk threshold. To determine this threshold, the risks should be compared with the risks of study interventions aimed at pathophysiology (28) or with the risks of procedures with diagnostic or therapeutic intent in clinical practice (38). It is argued that sham interventions will probably not exceed a risk threshold, because in general, the morbidity of surgical interventions is decreasing (38), and use of minimal invasive procedures will not exceed this limit (2).

Empirically, a recent systematic review has shown that the risks of adverse effects associated with placebos in surgery trials are small (61).

Arguments against acceptability of a sham control

A sham control is often unnecessary for scientific validity

The first argument against the acceptability of a sham intervention is that it does not per se increase the scientific validity of a trial. Correcting for placebo effects might be unnecessary, because the extent of placebo effects is often exaggerated (60). Furthermore, sometimes sham-controlled studies are conducted, while relevant results could also have been obtained by using the standard of care or no intervention as a comparison, although the results could thereafter, still require a sham intervention to confirm efficacy (30;62). Others criticize the simplistic way in which sham-controlled trials are performed currently, because the different components of a surgical procedure are not tested separately(51). A more complex trial design with various arms is required to truly determine what causes the effect of an intervention.

A sham control does not increase benefits to society

A second argument is that the comparison of an intervention with a sham procedure does not show whether the interventions will be an advantage to the current clinical practice, because sham procedures will not be implemented in clinical practice. It is more useful to perform trials without sham controls to show whether the intervention is superior or inferior compared to usual practice (51;52;63-65). Because sham procedures are not always necessary scientifically, public money will be spent unnecessarily, because surgical trials are expensive(65).

Risks and harm to a sham control group are unacceptable

A third argument is that the risks of sham interventions are not acceptable. Four different reasons are provided. First, it has been argued that the lack of chance of potential therapeutic benefits fails to be consistent with the duty of physicians to act in the best interest of participants, which is inconsistent with the Declaration of Helsinki (60;63;66;67). In contrast, other authors maintain that this argument conflates the ethical principles of research with the principles of clinical practice, because the goal is not to provide medical treatment to participants (28). Second, it is argued that risks in these trials are unacceptable, because risks are often not minimized. One author poses the argument that risks are not minimized when individuals are exposed to risks without any potential individual benefits (68). Third, others argue that sham interventions violate the standard of minimal risk (according to the US Federal regulations for Human Subject Research), i.e. that the risk are not higher than one encounters in daily life or during routine physical or psychological tests/examinations (66;68;69). In contrast, proponents of sham controls state that in general, this is not an appropriate argument for clinical research with competent adults (28). Fourth, risks are considered not reasonable in relation to the expected benefits for society, for which most use the example of the trial with fetal stem cells for Parkinson's disease (67;68). Some authors

have stated that reaching a proportionality between risks for the participants and the benefits to society offers little guidance for decision making and may lead to the risk of exploitation of participants for the sake of scientific knowledge (62). While some authors acknowledge that benefits for the sham group could occur, these benefits should not be taken into account in the risk-benefit ratio, because the placebo is used to control for placebo effects and not to assess therapeutic activity (2;27;68).

Difficulties in obtaining valid informed consent

A fourth objection to use a sham control is that adequate informed consent is more difficult to obtain in sham-controlled trials, due to the inherent risks and a high deviation from the standard of care (33). Some authors have suggested that participants in these trials have a greater risk of not really appreciating or understanding all the potential implications of a sham control: many participants may have the misunderstanding that the purpose of research consists of providing medical care, instead of gaining scientific knowledge (also known as the therapeutic misconception) (68-70). Some authors have hypothesized that participants may actually think that an invasive intervention will not be performed if it does not have any potential benefits, especially if a surgeon is to perform such an invasive intervention (38). Furthermore, it is suggested that a substantial misestimation of risks and benefits by the participants could occur (68).

Counter argument: Gaining valid informed consent is possible

These aspects, however, are not necessarily contra arguments, but can be used to stress that informed consent procedures need more safeguards. These safeguards could ensure that the implications of participating in a sham-controlled trial is explained sufficiently (2). Others state that often it might even be unreasonable to assume there are specific difficulties in obtaining a valid informed consent in sham-controlled clinical trials (28).

Moral discomfort for investigator and participant

A fifth argument is the possibility of moral discomfort raised by the possibility of active deception, both for the investigator performing the procedure and the participant. Sometimes the investigator (which can be the treating surgeon) performing the procedure is aware of the participant's allocated arm, and the investigator has to pretend providing the 'real' intervention. Hence, the investigator has to actively mislead the participant by pretending to perform the procedure, which could raise moral discomfort to the investigator, especially when having to continue the potentially misleading dialogue after the intervention (34;46;54;68;71). If the participant is not sufficiently informed of these deceptive strategies, this approach violates the principle of respect for persons, and their autonomous decision-making (72). Furthermore, some also maintain that participants will become patients when involved in these types of trials due to the creation of a wound. If harm to a participant occurs,

the investigator (often a surgeon) is likely to be regarded as the direct cause of the adverse event, raising the moral stress of the investigator (46;73).

Counter argument: Active deception is not a priori unethical

However, potential moral stress due to the need for misleading dialogue from the investigator can be relieved if the investigator performing the procedure and the one who does follow up and outcome assessment are separated (34). In addition, it should be taken into account that sham interventions are part of clinical research and not medical practice, even if the investigator is a surgeon. Furthermore, violation of the autonomy of participants can be prevented if a research participant is clearly informed beforehand of the chance of being in the sham control group (54).

Lack of support by public and researchers

Another potential objection to the use of sham interventions is the aversion of both the public and investigators toward sham interventions, which influences the feasibility of performing sham-controlled trials(74). Some state that empirical research indicates that some patients are unwilling to participate in placebo trials(66), while others argue that patients' views are lacking in the debate (75).

Counter argument: sufficient support exists

Currently, there are mixed opinions, because many patients are willing to participate in these trials (41;66;76-78). Furthermore, empirical research has shown support for sham interventions by investigators, both surgeons and anesthetists (66;71;79;80). Others propose that more studies need to be conducted that explore the attitudes toward sham controls (74), and the public should be educated about the need of a sham control (60;68;81). The resistance toward a sham intervention might also be mitigated by using different linguistics, by at least avoiding the negative word 'sham' (82).

Discussion

Six sets of arguments appeared from the literature: scientific validity, benefits to society, the risks and harms, informed consent, the use of deceptive tactics, and feasibility. We noted four patterns concerning the arguments for and against the ethical acceptability of sham procedures (Table 1).

Table 1. Arguments in favor and against the ethical acceptability of sham interventions

Arguments in favor	Arguments against
A sham intervention increases scientific validity	A sham intervention is often unnecessary for increasing scientific validity
A sham intervention increases benefits to future patients and society	A sham intervention does not always increase benefits to society
Risks and harm of a sham intervention can be acceptable	Risks and harm of a sham intervention are unacceptable
Gaining valid informed consent is possible	Difficulties are present in obtaining a valid informed consent
Active deception is not a priori unethical	Moral discomfort for investigator and participant can occur, mainly due to active deception
Sufficient support by public and researchers exists	There is a lack of trust and support by public and researchers

First, it appears that in comparison with other clinical research, no *significantly different* arguments are provided, even though sham interventions have a unique combination of specifics: the exposure of participants to "positive harm" without a chance of individual benefits, and the need for active deception. Sham interventions do not only involve a chance of harm of omission due to withholding a treatment (if an established effective intervention exists) like in oral placebos, but also a degree of harm and risks because the bodily integrity is affected by definition, also called "positive harm" (2;60). This concept, however, is not different ethically from the positive harm without direct potential benefits for the participants in other clinical research, such as phase I trials, especially when these involve first-in-class drugs (83-85). First-in-class drugs are drugs with a novel mechanism of action in comparison with existing drugs (84). Furthermore, active deception occurs in other types of clinical trials, which is considered acceptable when the participants are informed beforehand of the possibility of being exposed to deceptive tactics, so the participant can consent to its use (86). Furthermore, in (oral) placebo controlled trials, similar concerns have been raised regarding the extent to which this approach actually increases the scientific validity, particularly when a standard of care is available (87;88). Nevertheless, ethical guidelines show considerable agreement that placebo-controlled trials are necessary scientifically and valuable for society in certain instances, and it is likely that these situations are comparable to sham interventions (89-91). Therefore, it may be inappropriate to treat sham-controlled trials as a categorically different type of clinical research.

Second, although no difference in kind exists, the combination of specific features of sham interventions leads to a *difference in degree* in comparison with other research. For example, due to the inherent risks and harms involved and the involvement of deceptive tactics,

the informed consent procedure is more likely to be complex and needs a specific type of attention.

Third, although we presented the arguments 'in favor' and 'against' employing a sham intervention group, the two extreme positions, which range from 'sham interventions are always acceptable' to 'sham interventions are never acceptable', are rarely, if ever, defended. Moreover, almost no author fully condemns sham interventions. To begin with, the main arguments against sham interventions are provoked due to the risks and/or harm of a sham intervention, but these arguments were directed primarily at the fetal stem cell trials for Parkinson's disease (68;69). While these trials were considered morally problematic due to the high risks involved and the alternative scientific designs, this argument does not imply that sham-controlled trials always involve unreasonable risks. Furthermore, although some critics doubt the need of sham procedures to increase scientific validity and, subsequently to increase benefits to science and society, these critics argue that a sham control is used more often than scientifically necessary. Furthermore, they suggest that also pragmatic trials, in which the intervention is compared with the standard of care, are important, because these types of trials ensure information about the effectiveness in daily clinical practice (92). Hence, hardly any disagreement exists that sham interventions are scientifically necessary in certain instances. The argument of substantial benefit to future patients and society is not a separate argument but determined by the scientific validity; if a sham intervention increases the scientific validity, it also increases the benefits to science and society. Besides, the argument of the aversion of the public is mainly an argument of emotion, which (alone) is often not a strong enough argument to consider the practice unacceptable. In addition, it is reasonable that there is potential moral stress for investigators and participants due to the need of deceptive tactics, but many of the authors also showed ways to lessen the moral stress, also since sometimes the investigator can be blinded. Lastly, the argument of the difficulties in obtaining valid consent is not a strong argument because measures can be taken to find out whether the participant has understood the information sufficiently.

Fourth, it appears that most regard sham interventions as *conditionally acceptable*. These conditions consist of: scientific necessity, reasonable risks (in terms of: a proportional risk-benefit ratio), and valid informed consent. To ensure a valid informed consent, information about the chance for deception should also be provided, also called "authorized deception" (70). Regarding the assessment of the conditions of scientific necessity and reasonable risk and/or harm, various criteria in literature are presented.

We conclude that sham-controlled trials should not be treated as a categorically different type of clinical research but rather as different in degree. Further debate should no longer address whether a sham control is ethically acceptable, but rather when the conditions are fulfilled. Particularly attention should be paid to *when a sham intervention is scientifically necessary* and *when risk and harm are reasonable*.

The question when a sham intervention is necessary scientifically should be addressed by clear methodological criteria. Although placebo-controlled trials are often regarded as trials

that ensure the highest level of scientific validity, one should avoid the belief that placebos or sham interventions are considered a *goal*, instead of *means* to blind participants (and investigators) to prevent certain types of bias. If blinding a patient and/or the investigator is considered scientifically necessary (93), one should assure that the blinding is maintained during the trial to prevent bias as much as possible (94), and also to ensure that this is reported adequately in order to achieve comparability of trials in systematic reviews.

Nevertheless, even in double-blind RCTs, biases can still occur, e.g. different investigators can elicit different placebo responses (95). Furthermore, one should remain aware that double-blind RCTs often assure precision and generality, but realism is not always achieved, because the setting of a trial does not necessarily reflect the situation in clinical practice (96). Furthermore, an RCT might not be feasible for several reasons; when a long follow up time is required to assess intervention effects, when only a small number of patients are available, or because of patient preferences (25;97-100). In these situations, cohort or case control studies, based on registries, might be more appropriate (24).

An important criterion to determine the reasonableness of risks of a sham procedure is to consider whether the risks and/or harm (not only physical, but also psychological) are proportional to the benefits to science and society (85;101). Aspects that determine the societal benefits are the seriousness and prevalence of the disease (102;103). Assessing whether the risks are proportional to societal benefits is challenging because societal benefits are 'often vague, indeterminate and uncertain' (104). Several frameworks have been developed to assist researchers and IRBs in assessing the risk-benefit balance, such as the 'net risk test' (105;106) or addressing this challenge via decision theory (107). Assessing the reasonableness of risks and benefits is a task for both the researchers and the IRBs, but the IRBs should make the final decision, before the potential participants are given information about the risks and potential societal benefits (108). Hence, only sham-controlled trials with reasonable risks should be proposed to participants, instead of leaving the participants to determine the reasonableness of risks. In addition, some sham procedures will not lead to any substantive risk and harm, because these sham interventions involve only a minimally invasive intervention such as an intravenous or intra-articular injection. For other more invasive sham interventions, the risks of the sham procedure should be minimized by withholding a part of the intervention and, if possible, without de-blinding.

Another aspect that should always be considered is whether a standard of care exists. Even if a sham procedure might be scientifically necessary and its risks might be proportionate to the benefits, withholding the standard of care could be viewed as unacceptable. However, withholding the standard of care is acceptable when this would not add any risk of serious or irreversible harm to the participants (89;91).

Concluding remarks

We have ethically evaluated the arguments in favor and against sham interventions as they appear in the literature. We conclude that none of the published papers on this topic fully reject sham interventions, and many regard sham interventions acceptable provided the conditions of scientific necessity, reasonable risks, and a valid informed consent (including authorized deception) are fulfilled. We suggest that further debate should no longer address *whether* a sham intervention is ethically acceptable but rather *when* these conditions are fulfilled. In particular, the issue about when a sham intervention is necessary scientifically and when the risks and harm are reasonable should receive further interdisciplinary discussion.

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Chapter 8.

Choosing the appropriate comparator in Regenerative medicine trials: ethical points to consider

Submitted

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Abstract

The translation of Regenerative Medicine (RM) interventions, including cell-based interventions, biomaterial implantation, gene transfer and tissue engineering, from preclinical studies to clinical studies is increasing. This new era in science raises novel ethical challenges. One of these challenges concerns the appropriate choice of the comparator in (randomized controlled) trials aimed at testing efficacy, including the ethically contentious use of invasive placebos. Some guidelines regarding the choice of the comparator exist, but they require refinement as they are not specific for RM, are insufficiently comprehensive, or are only applicable to specific domains of diseases. In this chapter, we discuss the ethics of comparator selection in RM trials. First, we make a classification of RM interventions according to seven objectives: prevention, return to a healthy state, postpone surgical treatment, supplement surgical treatment, substitute surgical treatment, improve surgical outcome, and slow progression. Subsequently, per objective, the accompanying ethical points to consider are discussed. We argue that a sham procedure is an ethically acceptable comparator in RM trials with certain objectives, but is less appropriate for RM interventions aiming at preventing disease or substituting a surgical treatment.

Introduction

Suppose you as a researcher aim to investigate the efficacy of a stem cell injection in patients with early stage intervertebral disc disease. Is it ethically acceptable to allocate participants to an invasive placebo (sham) procedure in a stem cell-based randomized controlled trial (RCT)? Or suppose you are a member of the Research Ethics Committee (REC) and you have to review a research protocol in which participants with chronic heart failure are randomized to either a stem cell injection in the myocardium, or an injection with saline fluid. Would you give this trial ethical approval? These are two examples that illustrate the recent challenges clinical scientists and RECs face when choosing or evaluating the appropriate comparator in a clinical trial exploring a Regenerative Medicine (RM) intervention. RM is an umbrella term for a variety of techniques, including cell-based interventions, biomaterial implantation, gene transfer and tissue engineering (1-4). Due to the characteristics of RM interventions, such as the invasive nature, the usage of some interventions in early stage, and the novelty and hype of the field a new light is shed on certain ethical challenges (5;6). One of these challenges concerns the appropriate choice of the comparator in RCTs. Some tools of support regarding the choice of the comparator in these clinical trials exist, but they require refinement since they are neither specific for RM (7-10) nor comprehensive. This lack of comprehensiveness is highlighted by guidelines focusing on only one type of RM intervention (11-14), or on specific domains of diseases (15-17). This lack of ethical standards creates difficulties for scientists and RECs when designing or evaluating RM clinical trial protocols. This could also explain the diversity in the use of controls in current trials. For example, in the cardiovascular field a large variety is seen in different trials investigating similar cell-based interventions (18-20). In this chapter, the ethics of comparator selection in RM trials is discussed. First we make a classification of the stages in disease development and show which objectives of RM interventions can be distinguished in these different stages. Subsequently, per objective the main accompanying ethical considerations will be discussed. This chapter focuses on the challenges in the choice of the comparator for trials aimed at showing efficacy of the RM intervention, via the use of a randomized trial design.

Stages in disease and the objectives of RM interventions

The natural course of a disease over time can follow a staged pattern, progressing from mild to worse. Four main stages can be identified: 1) *at risk of the disease*, 2) *early stage disease* with minor symptoms, *3) surgery indicated* and *4) late stage disease* with severe symptoms and no other options. Included in the term 'surgery' are also minimal invasive interventions. Examples of disorders in which these stages can be distinguished are degenerative disorders like osteoarthritis, Alzheimer's disease, Parkinson's disease, diabetes type II, and macular degeneration. Not all disorders follow this disease pathway as some not necessarily gradually

progress, but merely can be classified as acute or chronic, and/or as mild or severe. Examples are traumatic lesions (e.g., spinal cord injury), and certain cardiovascular disorders, for example coronary artery disease, and stroke. The acute phase can bear resemblance with the characteristics of early stage disease, and the chronic stage with late stage disease, although this is not always the case. RM interventions are currently being developed for the full range of these different stages, and in all these stages *one or more objectives* can be discerned. Accordingly, seven types of RM interventions can be defined (Figure 1). In an *at risk* stage of disease, the objective of the intervention is prevention, while in an *early stage* of disease the objective is return to a healthy state, or at least slowing progression of disease. A RM intervention applied at the moment that *surgery is indicated*, can be aimed at substituting the surgical treatment, or at supplementing surgical treatment. Other interventions are applied before surgery and aimed at postponing surgery, or are applied post-operatively and aim to improve the outcome of surgery. RM in a *late stage* disease without any other surgical options is aimed at slowing progression of disease or even restoration of function. Especially RM interventions for early stage disease are still in the preclinical phase of development, while the others are also in the clinical trial phase.

The main types of comparator in RM clinical trials

The preferred method of establishing an intervention group and a control group that allows an unbiased comparison regarding efficacy is via randomization (7;8). In this chapter we focus on the stage of translation of RM interventions in which successful safety and small efficacy studies have been conducted and in which an RCT is the next step. Although conducting RCTs for invasive interventions involve practical and ethical hurdles, the RCT is the default when the objective is to assess efficacy of an intervention (21-23). The main types of comparators in RCTs are *placebo, standard of care* (e.g., a conventional surgical procedure, another RM intervention, a drug, pain management, standard exercise therapy*),* or *no intervention*. A placebo as a comparator can also be applied within an add-on design, which means that it is provided on top of standard treatment that all participants receive. Placebos are assumed necessary to increase the validity of testing efficacy, particularly when clinical endpoints are incorporated in the trial, such as pain and quality of life (24). A placebo allows for blinding which assures that both the participants and investigators are unaware of the allocated intervention. Via blinding the effect of the tested intervention can be distinguished from an effect caused by non-specific effects, such as placebo effects and reporting bias (25). Non-specific effects can occur in 'traditional' drug trials, but due to high expectations of RM among participants and researchers, these effects could be increased. As RM interventions are invasive interventions, a placebo that optimally blinds participants and investigators (the one providing the intervention) requires an *invasive placebo*, also called a *sham intervention*. In the case of autologous cell transplantation (cells of the participant him- or herself), a fully

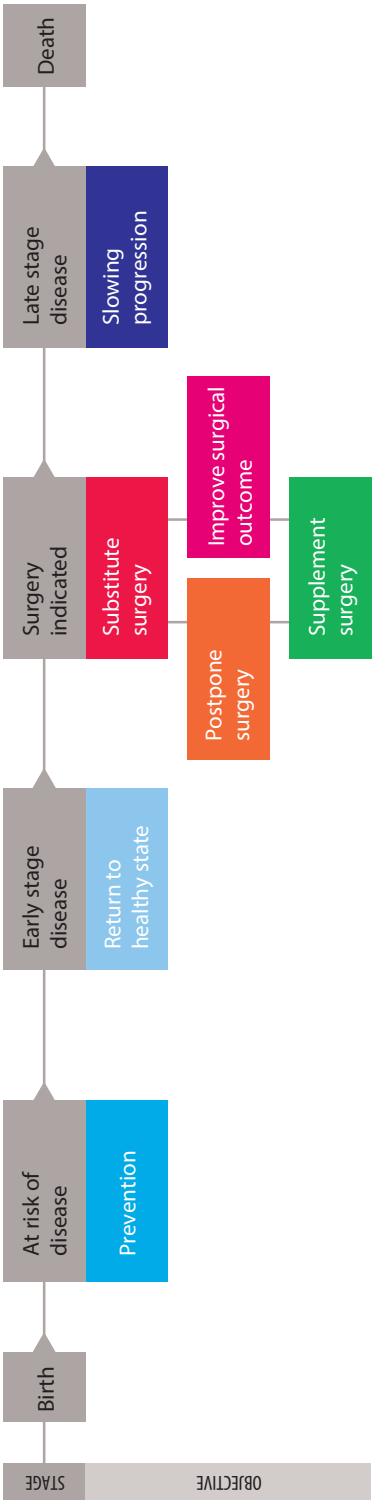

Figure 1. The seven objectives of RM interventions, and the related stages of disease

mimicked intervention requires both conducting the harvesting of cells and a sham delivery. In RM trials, the use of an invasive placebo also allows to consider the effects caused by the insertion of a surgical instrument (e.g., scope, needle) and/or its accompanying fluid or gel (26;27). A part of the effect attributed to the stem cells, gene transfer, or biomaterial implantation can be due to the local (inflammatory) response of the host. We will call these effects "insertion effects". Especially since the RM field is an upcoming field accompanied by new uncertainties (28) it is not yet known to what extent these effects can occur, rendering it important to take these into account in an explanatory trial design. This is most likely to be achieved when the sham procedure fully mimics the RM intervention.

Main ethical considerations in the choice of the comparator in RM trials

The use of a sham intervention as a comparator raises ethical debate. In a recent letter to the editor, sham interventions were even called 'ludicrous' based on the risks without potential therapeutic benefits for the participants (29). An important aspect that determines the ethical acceptability of a sham is whether a best proven or established effective intervention exists (9;10). The term 'best proven' intervention refers to an evidence-based intervention, in contrast to an 'established effective' intervention, which is consensus-based (30). Although there is controversy around the exact interpretation, at least '[..] the control group shall not be denied a superior medically established procedure that has net clinical relevance for a specific condition.' (30). According to the Council for International Organizations of Medical Sciences (CIOMS) guidelines and the World Medical Association Declaration of Helsinki, withholding standard of care could be acceptable when this would not add any risk of serious or irreversible harm to subjects and only the use of a placebo would lead to scientific valid results (9;10). The specific aspect of invasive placebos, in contrast to placebo pills, is that inherent risks (and uncertainties) are involved due to the insertion. Also co-interventions related to the (sham) surgery could be part of a sham procedure and provoke risks, such as the use of antibiotics (31). When designing or evaluating a trial, one has to determine whether the risks (and uncertainties) of the research interventions involved are proportionate to the potential benefits, i.e. a risk-benefit assessment needs to be made. An important difference between the trial arms in a sham-controlled trial is that the sham group can experience risk without any perspective of direct benefits. Hence, the risks of this trial arm need to be in balance with the improvement the intervention is expected to have for society, also called anticipated social value or aspirational benefits (9;10;32-34). Factors that, for example, determine the risks of the sham are the invasiveness of the RM intervention, while the benefits are determined by the severity and prevalence of the disease. Here, we only provide points to consider regarding the risk-benefit evaluation of the sham group, but in the final decision-making-process, researchers and RECs also need to take into account the total risks and benefits. A risk-benefit assessment also consists of risk treatment which means that

one should modify the risks and enhance the potential benefits (35). For example, the risks of the sham could be minimized by not fully mimicking the invasive RM intervention, unless this highly compromises the scientific validity. Benefits could be enhanced by also collecting knowledge on the working mechanism of the RM intervention (36).
Another condition for determining the acceptability of sham is whether valid informed consent can be obtained by taking the elements of disclosure, competence, and voluntariness into account (37). It has been suggested that the use of an invasive intervention, such as sham, could foster therapeutic misconception (TM) (38). In TM, the participant confuses care with research which could compromise a valid consent. TM may especially occur in the field of RM, where expectations of researchers and participants are high (39). Therefore, especially in sham-controlled RM trials one should take safeguards to decrease the chance of TM, for example, by prolonged reflection time, re-evaluation of understanding prior to inclusion and during a trial, and avoiding confusing linguistics (40;41). In general, efforts should be made to enhance understanding, both through the content as well as the manner of providing the information, for example by enhanced consent forms, and extended discussions (42;43). Furthermore, one should be aware whether the potential participant is in an acute or chronic stage of disease: a participant with a recent onset disease might not fully understand the consequences of participating due to anxiety and stress, and also voluntariness might be impaired (44). In participants with chronic disease, the competence and voluntariness is less expected to be compromised.

Ethical points to consider per RM intervention

Objective: prevention - Stage: at risk of disease

In the near future, RM interventions are expected to be used for disease prevention, which requires testing in individuals who are susceptible for developing clinical disease. These so called 'potential future patients' do not yet suffer from symptoms. In the field of orthopedics examples are individuals with incidental findings of radiographic osteoarthritis but without pain or dysfunction (45). In the cardiovascular field, examples would be individuals with multiple risk factors without having experienced a cardiovascular event yet. These risk factors could also include genetic mutations or elevated biomarker levels, of which some of these may strongly relate with disease, while others may have a limited predictive capacity (46;47). An example in the neurological field in which prevention trial with medication occur are asymptomatic individuals at high genetic risk of Alzheimer's disease (48).
The standard of care for these individuals consists of a preventive regime of lifestyle measures such as exercise, and/or preventive medication. When this regime is established effective, one should provide this to the control group. However, when many placebo effects or bias are expected a sham-controlled (add-on) design for testing the efficacy of these interventions is scientifically preferable. Nevertheless, establishing a proportional risk-

benefit ratio to the sham group is challenging. The risks of an invasive placebo are relatively high (although this depends on the invasiveness of the RM intervention), as these healthy participants have much functionality to lose and harms can have long-term consequences. The anticipated social value of the intervention depends on the nature and magnitude of the improvement the intervention is expected to have on the wellbeing of patients (32). For preventative RM interventions, this means that the correlation between (observed) degenerative changes and clinical disease should be strong; if only a small proportion of asymptomatic individuals would develop the disease, the anticipated social value would be small. Further, the potential benefits to society of developing preventive RM interventions could be high from a cost-effectiveness perspective, although costs could also increase as people enter the health care sector earlier. In addition, preventive interventions could have unwanted impacts on society in terms of a changing experience of sickness, as participants will be regarded sick while hardly any manifestation of disease is apparent (49). Hence, the benefits of these trials to society are relatively uncertain. Another aspect that determines the ethical acceptability of sham is whether adequate informed consent can be obtained. Since "potential future patients" are healthy, the likelihood that participants can voluntarily decide whether to participate is high, and their competence is not likely to be compromised due to underlying illness. However, disclosure of information could be difficult as patients should be informed about the probability of developing disease, receiving the sham intervention, and the probability of harm. As it is suggested that persons have difficulties with understanding the concept of probabilities, especially when explained in percentages, this could lead to misunderstanding and compromise a valid consent (50;51). Due to the high risks of a sham intervention, the uncertainty of anticipated social value, and the difficulty of gaining valid consent the first choice of the comparator is standard of care.

Standard of care can be considered to be the most appropriate comparator for testing RM interventions aimed at prevention.

Using a sham intervention as a comparator is not likely to be ethically appropriate since:

- the risks of losing functionality in these healthy participants is high and are not likely to outweigh the uncertain benefits to society
- assuring a valid informed consent is complicated due to the probabilities involved which complicate disclosure and could lead to misunderstanding

Box 1. Points to consider for RM aimed at prevention

Objective: return to healthy state - Stage: early stage disease

RM interventions are also developed for individuals in an early stage of disease with the aim to return these patients to a healthy state or at least to slow disease progression. These individuals suffer only from minor symptoms (5). Examples in the field of orthopedics are

patients with starting knee complaints or low back pain, and in the cardiovascular field, patients that have endured a relatively small myocardial infarction without post-MI systolic dysfunction (52;53). In the neurological field, examples include patients with mild symptoms of Alzheimer or Parkinson's disease.

If available, the standard of care in this group can exist of pain management, preventative medication and/or lifestyle measures. One could consider withholding standard treatment (temporarily) and using sham interventions as a control, if this does not lead to serious harm and is scientifically necessary. Another option is to use an add-on design, if the standard of care cannot reasonably be withheld. The risk of losing functionality due to sham is high as the patients are relatively healthy. However, as it is likely that the disease will progress in the future, developing RM interventions for these disease stages leads to high anticipated social value. Especially when the sham intervention is not highly invasive, the risks could be proportional to the benefits to society. Similar to the previous category, the likelihood that participants can make a voluntary decision to participate is high, and their competence is not likely to be compromised due to underlying illness. However, the disclosure of information can be complicated, although less uncertainties are present compared to the 'at risk' group.

The most appropriate comparator for RM interventions aimed at returning to healthy state can be considered to be a sham intervention. A specific aspect to take into account is that the disclosure of information regarding probabilities requires extra safeguards

Box 2. Points to consider for RM aimed at returning to healthy state

Objective: postpone surgical treatment - Stage: surgery indicated

A set of RM interventions has the aim of postponing time until a surgical procedure. Developing such interventions could be beneficial when the available procedure is successful, but has some long-term disadvantages. For example, using a RM intervention to delay the need for total knee prosthesis in young and active patients falls into this category. Such RM interventions for cardiovascular disorders are less likely to be developed, while in a neurological disease like Parkinson's disease such a RM intervention could be applied before deep brain stimulation is an option. The endpoint 'time until surgical procedure' is often favorable in these trials. Therefore, using a surgical procedure as an active control is not informative. In current practice, the endpoint is known to be both patient and physician driven, and thus influenced by subjective factors (54), and therefore prone to placebo effects. As a consequence, the optimal comparator is a sham intervention.

The magnitude of risks depends on the consequences of delaying the surgical procedure and whether the sham intervention could affect the possibility and successfulness of the surgical procedure. For example, delaying time to a joint replacement in participants with chronic

knee osteoarthritis will expose participants to more pain. However, when the pain is of a mild nature or can be mitigated via pain management, no serious risks exist. However, when the disease is far developed and painful, it is more urgent to conduct the surgery.
The anticipated social value can especially be considered high when the standard surgical procedure has many disadvantages. When these potential benefits to society are high, these could outweigh the risks. An alternative is to provide no intervention or standard of care (e.g. pain management) to the control group.
A specific aspect to take into account in the disclosure of information is that the control group is not able to receive the RM intervention, if proven effective after completion of the trial. This is due to the fact that a part of participants will already receive the surgical procedure during the trial. No other specific aspects are expected to influence the conditions of informed consent.

The most appropriate comparator for RM interventions aimed at postponing surgical treatment can be considered to be a sham intervention. A specific aspect to take into account is that one should disclose to the participants that the sham group might not be able to receive the RM intervention, if proven effective.

Box 3. Points to consider for RM aimed at postponing surgical treatment

Objective: supplementing surgical treatment - Stage: surgery indicated

Certain RM interventions are developed to supplement an existing surgical treatment in order to improve efficacy or its safety. An example of a trial that has been conducted in this field is the addition of autologous cells to core decompression surgery for osteonecrosis of the femoral head (55). Another example is the supplementation of stem cells to coronary bypass artery graft (CABG) (56;57).
If a sham intervention is scientifically necessary for testing efficacy it is most appropriate to use a sham intervention on top of the surgical procedure, i.e. an add-on design. For example, when the intervention is applied while the patient is conscious, such as in a catheterization procedures, a sham procedure on top of the procedure is required to blind the participant. An accompanying advantage is that it allows blinding of both the patient and the investigator and correction for insertion effects. In addition to the inherent risks of the sham, risks due to a prolongation in operation time exist, but in total, these risks are not considerably high. The anticipated social value of these supplemental RM interventions is especially high when the current surgical procedure is suboptimal and allows for improvement of outcome. This shows that for these types of RM interventions, the potential benefits could outweigh the risks of the add-on sham intervention.

Regarding the criteria that determine a valid informed consent, one should take into account whether it concerns a chronic or acute stage in which the surgical intervention is applied, as earlier explained.

The most appropriate comparator for these RM interventions aimed at supplementing surgical treatment can be considered to be a sham procedure on top of the surgical procedure. A specific aspect to take into account is that patients in an acute stage of surgery may not fully understand the consequences of participating due to anxiety and stress, and also voluntariness might be impaired

Box 4. Points to consider for RM aimed at supplementing surgical treatment

Objective: substituting surgical treatment - Stage: surgery indicated

The objective of some RM interventions is to substitute an existing surgical procedure. Interventions in this category are mainly developed to provide a more effective or efficient procedure. Examples are the development of autologous chondrocyte implantation (a RM intervention aimed at treating damaged knee cartilage) as an alternative for microfracture (58), or the use of growth factors in spinal fusion procedures (59). From a scientific point of view it is relevant to gain scientific knowledge regarding relative efficacy, which can be achieved by comparing the RM intervention with the available surgical procedure, provided the latter has net clinical relevance. Furthermore, the choice for this comparator minimizes risks to the control group as no standard of care is withheld. However, determining whether placebo effects or other biases determine the efficacy is difficult as blinding patients and investigators is not always feasible since the procedures may require different surgical modalities (22). At least, one should consider blinding the outcome assessors, by allowing a separate team to perform the follow-up.

When the current surgical intervention is considered effective, an important scientific consideration is whether the RM intervention is that far developed that it might be as effective as the current procedure. In the early development phase of a surgical technique, the learning curve of the surgeon may still affect outcome. This imbalance in expertise could lead to an invalid comparison between the existing and novel intervention (22). Therefore, one should assure that the RM intervention has completed early safety and efficacy stages to allow proper comparison with the existing procedure, both to increase scientific validity and to prevent unnecessary risks to the participants. The described challenges (and additional ones) are similar to trials testing existing surgical interventions against novel surgical procedures (22).

The most appropriate comparator for RM interventions aimed at substituting surgical treatment can be considered to be the existing surgical treatment, because this allows showing relative efficacy. It is also favorable to include an independent outcome assessor or to separate the post-procedure patient care team to blind the outcome assessor

Box 5. Points to consider for RM aimed at substituting surgical treatment

Objective: improving outcome of surgical procedure - Stage: surgery indicated

Some RM interventions aim to improve the outcome of a procedure with application shortly after the intervention. A recent example in the field of orthopedics is a RM trial that evaluated the effect of adult mesenchymal stem cells via intra-articular injection to the knee following partial meniscectomy (52).

In order to gain knowledge on the efficacy of these interventions, a sham intervention as a comparator is indicated. In addition to the inherent risks of the sham, the risks depend on the time between the surgical procedure and the sham, as the sham could affect the recovery from the surgical treatment. Next to that, the burden for the participants is high as they just underwent a surgical procedure of which they are recovering. One criterion to determine the anticipated social value is whether the current surgical procedure is unsatisfactory. Hence, the likelihood that the risks are proportional to anticipated social value increases when the time between the surgery and the sham intervention is relatively high, and the outcome of surgery requires improvement.

The validity of informed consent could be compromised as the perioperative period is a stressful period, which might impair understanding, especially in combination with a sham procedure.

The most appropriate comparator for RM interventions aimed at improving surgical treatment can be considered to be a sham intervention.
A specific point of concern is that understanding of the participants might be impaired as they are in a stressful period.

Box 6. Points to consider for RM aimed at improving surgical treatment

Objective: slowing progression - Stage: late stage disease and no other options

The majority of RCTs in RM are targeted at patients in late stage disease, for example patients suffering from chronic heart failure, critical limb ischemia, and Parkinson's disease (18;31;60). From a scientific point of view, a sham intervention as a comparator is indicated in order to demonstrate efficacy. However, one should not withhold proper pain management or other

supportive care to the control group when this could lead to serious harm. In this case, one can consider the use of sham as a control on top off the standard of care.

The risks of sham interventions in this stage of disease are relatively low in comparison with individuals in an early stage of disease, as the participants have less chance of losing functionality since the disease is relatively far progressed (61). Nevertheless, the participants can still experience burdens, such as pain and disability. The anticipated social value conducting trials to test these interventions is high, as advanced stage participants are in much need of treatment and no other options are available. On the other hand the chance of benefits could below because of highly degenerative state (5;6), although this does not per se have to be relevant for tissue engineering products (5;6). Hence, due to the relatively low risks and the potential benefits to society, the risk-benefit ratio of a sham-controlled trial is considered to be acceptable.

However, the validity of the informed consent procedure could be compromised due to misunderstanding. In fact, these patients are often in desperate need for treatment which increases the risk that they confuse research with treatment, increasing the risk of TM (62). On the other hand, people with a late stage disease are often chronic patients and are likely to have adjusted to their disease which diminishes the risk of TM (63). However, the risk of TM is increased when participants are disclosed that they might receive the intervention (when they were randomized into the sham group) after completion of the study, if proven effective (6). One should avoid suggesting this to participants during the informed consent procedure if this risk is low due to high mortality rates(6). Furthermore, in neurological patients and certain cardiovascular patients, the illness can also impair the mental capacity to make an autonomous decision.

The most appropriate comparator for RM interventions aimed at slowing progression **c**an be considered to be a sham intervention. A specific aspect to take into account is that the risk of therapeutic misconception is relatively high in these participants and extra safeguards could assure a valid consent.

Box 7. Points to consider for RM aimed at slowing progression

Conclusions

As RM interventions differ from traditional drugs and surgical treatments, the comparator selection in RM trials requires specific recommendations for researchers and RECs involved. We have shown that the appropriateness of the comparator for a RCT is largely determined by the objective of the RM intervention. A sham procedure is the most appropriate comparator for the majority of these objectives but is less appropriate when the trial is aimed at prevention (mainly due to risks of the sham) or when an effective surgical treatment exists (as withholding the standard of care is unacceptable). For the other objectives of RM interventions sham interventions are preferable to test efficacy, not only to assure blinding but also to correct for insertion effects. Further, the inherent risks of the sham intervention could be acceptable when the participants do not have much functionality to lose and if the anticipated social value is high. As sham interventions can give rise to misunderstanding of participants, extra safeguards should be taken to assure a valid informed consent procedure. This is especially required in patients undergoing acute surgery and in a late stage disease, due to potential compromised competence and voluntariness. Although sham interventions are ethically contentious, they are essential to establish an evidence-based research field. Ethical points to consider in the choice of the comparator are provided for (clinical) scientists when they set-up of RM trials testing efficacy and RECs evaluating these trials. Compared to available literature, this chapter provides a comprehensive analysis of both the main ethical and methodological aspects of comparator selection. Further, this chapter facilitates compiling ethical standards for RM trials. As a consequence, more similarity in the choice of the comparator in RM trials can be established, which improves trial comparability. These considerations should be updated regularly as clinical trials give insight in consequences of RM interventions. In addition, when these general considerations are applied to a specific trial also other determinants like the specific characteristics of the disease, treatment alternatives, and of the RM intervention can influence the adequate choice of the comparator. In addition, future ethics research should analyze to what extent these standards are applicable to disorders without a gradual disease progression. Also analysis should take place on when RCTs are scientifically necessary and feasible for testing the efficacy of RM interventions, and when other trial designs are more appropriate.

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Chapter 9.

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

Under review

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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 characterized by their susceptibility for developing clinically manifest disease in the 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.

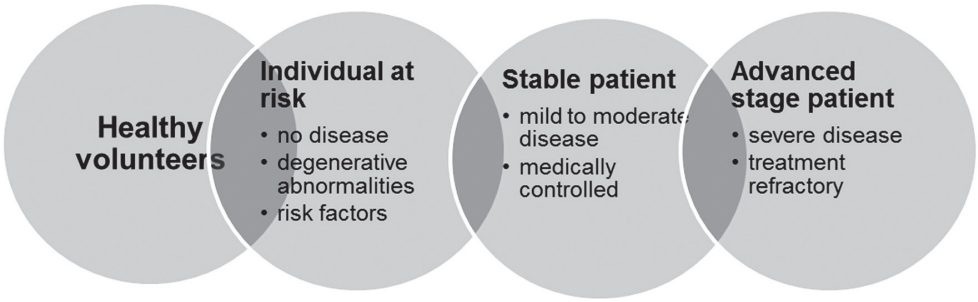
We conclude that selecting the model is not ethically justifiable for first-in-man trials with RM interventions due to the high risks and uncertainties. However, the model can be ethically appropriate for testing the efficacy of RM interventions under the following conditions: interventions should be 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

The emerging field of Regenerative Medicine (RM) aims to restore the function of damaged or diseased tissue by stimulating the body's own repair. A wide range of different techniques belongs to this field, including stem cell transplantation, tissue engineering, gene transfer, and biomaterials (1). Some of these techniques are regarded most effective when applied early in a disease process when aiming to prevent disease (2;3). In order to gain scientific knowledge on the effect of these preventive RM interventions, it is necessary to test these in individuals the intervention is aimed at: *individuals at risk.* These individuals are characterized by their possible susceptibility for developing clinically manifest disease in the future, but they suffer neither from symptoms nor disease at trial inclusion (Figure 1). There has been little debate about the ethics of selecting *individuals at risk* for clinical trials (3). Indeed, the debate on participant selection has been centred around three other participant models (i.e. participant populations in clinical research): the *healthy volunteer* model; the *stable patient* model; and the *advanced stage patient* model (Figure 1) (4-6). *Healthy volunteers* are often considered suitable to include in first-in-human (FIH) trials because they deliver reliable knowledge on safety, pharmacodynamics, and pharmacokinetics, due to a lack of co-morbidities of co-interventions (4-6). However, for (potentially) more risky first-in-human trials, patients are considered more appropriate than healthy volunteers. These patients can be either in a stable or advanced stage of disease (4;6). The *stable patient* model consists of patients with diseases that are medically under control, and which still have treatment options when enrolling in a trial. The *advanced stage patient* model consists of patients in the end stage of their disease, often without any treatment options left (2). This group of participants is often called the oncology model (6), although it also involves patients with disorders that are severely disabling but not life threatening. Selecting stable patients is sometimes preferred over advanced stage patients, among others, because the informed consent procedure is less likely to be compromised, and (side) effects are unlikely to be related to co-morbidities (4;6).

In this chapter we examine the ethical acceptability of selecting the *individual at risk* model for clinical trials examining preventative RM interventions. We will thus not focus on the desirability of developing such preventive RM applications, although this is a debate that should also be conducted.

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



The individual at risk model

At present, individuals at risk of disease are selected for low-risk trials that examine the effect of preventive medication or life style measures aimed at lowering risk factors (7;8). In contrast, In contrast, the often invasive and complex RM interventions are characterized by their relative high risks and uncertainties, and therefore RM trials often include the stable patient model or the advanced stage patient model. Rarely, healthy volunteers are considered an appropriate study population (9). However, in RM clinical trials examining the effects of preventing disorders, the selection of the individual at risk model will increasingly be considered. Especially for demonstrating *efficacy* and *effectiveness* one necessarily needs to test individuals at risk, as it is the only way to relate the intervention to the occurrence of a preventive effect. As such, this model coheres with the principle that the scientific objective should be one of the bases for determining eligibility when selecting participants for research, next to an appropriate balance between risks and potential benefits (4;10).
An example of this model in the field of orthopedics is the individual with (minor) radiographic knee osteoarthritis such as Kellgren-Lawrence grade I/II, that does not experience knee pain or dysfunction yet (11). Another eligible group are individuals having an increased risk of disc degeneration at adjacent motion segments due to undergoing surgery for disc herniation or spinal fusion (12). It is thus not individuals at risk in general that will be selected for RM trials, but a special subgroup of these individuals; individuals with some degree of degeneration, as it is likely that it needs to be present in a participant in order to allow for regeneration (13;14).

Challenges of the individual at risk model in RM

Three main challenges arise when selecting the individual at risk model for testing RM interventions.

The challenge of reaching risk-benefit proportionality

As individuals at risk have relatively much healthy tissue to lose, one can question whether it is justified to expose them to the risks and uncertainties of RM trials. Moreover, absent reduced life expectation, in contrast to advanced stage patients, these potential harms may have long-term consequences. Individuals at risk in clinical trials may have the additional risk 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 (3). On the other hand, similar to healthy volunteers, they may be better at tolerating physical risks due to their healthier status (4). Besides these *physical risks*, a clinical trial can also contain *psychological risks* (15). One of the psychological risks when selecting individuals at risk for RM trials is that they could start losing confidence in their health, as they are aware of potentially developing a disease in the future. Further, individuals may also feel pressured to undergo the potentially preventive intervention, as they can otherwise be blamed for getting diseased later in life (16). These psychological risks are not restricted to participants in clinical trials, but are applicable to RM interventions aimed at individuals at risk in general. As we have mentioned earlier, it does not lie in the scope of this chapter to examine the desirability of preventative RM interventions.

The risks and uncertainties could be acceptable if they are proportional to the potential benefits. The potential benefits of a trial mainly consist of aspirational benefits and direct benefits (17). Aspirational benefits, also known as the anticipated social value, depend on the nature and magnitude of the improvement the intervention is expected to have on the wellbeing of future patients (18). For preventative RM interventions this is partially determined by the relation between degenerative abnormalities (and other risks factors) and incidence of disease; if only a small proportion of the individuals would develop the disease, the anticipated social value would be smaller. Indeed, this relation is not self-evident in certain diseases, such as degenerative orthopedic disorders. *Direct benefits* are the therapeutic benefits of the tested RM intervention for the individual research participants. These benefits will increase with increasing relation between risk factors and clinical outcomes, in a similar manner as the anticipated social value. Individuals at risk will benefit longest if the intervention is effective as they have longer life expectancies, in a similar manner as they lose most when it turns out to be harmful (4).

Designing an efficacy trial for prevention is more complex

A second challenge is the complexity of the design of these preventive trials. To demonstrate the effect of the RM technology on prevention, a long follow up is necessary because disease still needs developing. 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 as well as 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 the individuals at risk, necessary to respect and protect the autonomy of participants. Informed consent contains five essential aspects: disclosure, understanding, competence, voluntariness, and consent (19). Although individuals at risk are in general competent, and their voluntariness is not hampered, 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 unclear if, when, and how individuals at risk will manifest clinical disease. In addition, the dilemma arises to what extent uncertainties should be *disclosed* (21;22).

Ethical acceptability of the individual at risk model in RM trials

Because of the relatively high inherent risks and uncertainties of RM, and the "healthiness" the individuals can lose, we have the opinion that individuals at risk should not be enrolled in first-in-human trials testing RM interventions. Enrolling stable patients could be appropriate when it concerns low risk RM interventions; for example, when the method is less risky (like local injections into non-organ tissues instead of systemic or intra-organ injections) and/or when considerable experience exists (with the product or its reference classes) (23). As first-in-human trials are aimed at examining risks and feasibility, it is not necessary to use individuals at risk to obtain reliable scientific results (although it would be easier to examine due to the absence of co-morbidities).

If preclinical studies show that RM interventions are expected to be most effective when applied in an early stage, it is unavoidable to demonstrate efficacy in individuals at risk. In this case, one should assure that this preclinical evidence is strong by adequate randomization and blinding (23). Further, since uncertainties decline during translation, the selection of the individual at risk model could be acceptable under certain conditions: when 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 order to increase the risk-benefit proportionality, the researcher should make efforts to minimize the risks and to enhance the benefits. Therefore, only a low risk RM intervention should be tested in this model. To increase the potential aspirational benefit of the trial, it is especially important that the trial targets diseases in which the at-risk phase most likely leads to clinical manifest disease in a short time period. In addition, this allows for a reduction in follow-up time and sample size which in turn, minimizes the overall risks and burden 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 (24). 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 (25). While these aspects determine the acceptability of individual clinical trials, debate should take place on the societal impacts of preventive RM interventions. These can contribute to the contemporary strong focus on health and disease in our daily lives and to medicalization of society (16).

Conclusion

We expect an increase in the use of the individual at risk model due to the development of 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 first-in-man trials with RM interventions as the uncertainties are too high. However, under strict conditions this model could be appropriate for efficacy trials: interventions should be low risk; the relation between degenerative abnormalities (and other risk factors) and clinically manifest disease should be strong and in a short time frame, or proper surrogate outcome measure should exist; strong preclinical evidence of efficacy needs to be present; and extra safeguards should be taken with regard to uncertainty communication in the informed consent procedure.

We believe that early initiation of the ethical debate on the challenges for selecting these individuals for research allows responsible innovation and is relevant for other new preventive technologies.

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Chapter 10.

General discussion

This thesis analyzed the ethical issues that arise when translating regenerative medicine (RM) interventions into clinical trials and society by using orthopedic disorders as an exemplary case.
In this chapter I will discuss and reflect on the main findings of this thesis with regard to the challenges of setting up RM clinical trials. In addition, I will evaluate the contribution of an empirical study to ethical analysis, and the role of ethicists in technology development. Lastly, I will put RM interventions in a broader societal perspective.

The challenges of orthopedic RM clinical trials

In **chapters 2** and **3** the main ethical challenges of setting up early orthopedic RM clinical trials were identified: the analysis and evaluation of risks and benefits; the choice of appropriate outcome measures and comparators; and the selection of the appropriate participant group. While these chapters focused on early clinical trial phases (phase I and phase I/II), these challenges are also relevant in late phase trials. Particularly the choice of the comparator is important in phase III trials testing efficacy.
These ethical challenges are not different in principle from "traditional" drug trials, but RM technologies place those challenges in a new context due to the main characteristics of the technology in combination with the characteristics of the aimed study population (1;2). In contrast to pharmaceuticals, devices, and other surgical procedures, RM technologies are novel, complex, invasive, and are aimed at regeneration. Further, as explained in **chapter 5**, the development of the RM field is characterized by high appeal and expectations. When combining these features of RM with the characteristics of the orthopedic study population, the usual ethical challenges get a new twist. Achieving a proportional risk-benefit balance is challenging as orthopedic patients are relatively healthy, while RM interventions are risky and uncertain due to their novelty and invasiveness. Furthermore, a challenge that arises is what should be the ultimate aim of RM research and which outcome measures correspond with that goal. Should RM research strive for regenerating tissue or merely for improving wellbeing of patients? In **chapter 3** it was shown that also biomedical professionals depicted this as an important challenge. We argued that in a developing field like RM it is important to combine both aims, as is also proposed in the ''translational model of value'' (3). Further, these questions can be viewed in the broader context of the concept of 'health': whether health should be defined as absence of disease (hence, absence of degeneration) or, for example, by the ability to realize one's vital goals, which merely focuses on wellbeing (4). I reflect on this aspect in the last paragraph of this chapter. Another ethical challenge that arises is the adequate choice of the comparator in a trial. A particular challenge is that using a placebo as a comparator in a RM trial requires an invasive placebo, which is even more ethically challenging than placebo pills. Further, the challenge rises which is the most appropriate participant group for enrolling in these risky clinical trials, which could range from early stage

disease patients to advanced stage disease patients. Next to the four challenges described in **chapter 2**, **chapter 5** demonstrated that the challenge of gaining adequate informed consent needs to be taken into account. Although this chapter mainly focused on cardiovascular RM trials, it is expected that this challenge is also relevant in orthopedic RM trials. An important component of informed consent is the disclosure of information. In the context of RM, future ethics research should particularly focus on how (and the extent to which) uncertainties should be disclosed to potential participants (5). Particularly the appropriate choice of the comparator and the participants was discussed in depth in this thesis.

The appropriate comparator in RM trials

An important challenge in designing atrial aimed at testing efficacy is the choice of the comparator: is the standard of care, placebo, or no intervention most appropriate? Since RM interventions are characterized by invasiveness, a placebo requires a placebo surgery or injection, also called sham intervention. Although placebo surgery has been used for a long time in clinical research, it is still an ethically contentious subject as **chapter 6** illustrated. Here we show that the comparator for cell-based interventions in cardiology differed among research groups; more than half of the total 56 RCTs did not incorporate a sham intervention. This diversity could be related to conflicting views on scientific necessity or ethical acceptability of sham interventions. In **chapter 7** it was shown that sufficient arguments exist to regard sham interventions scientifically necessary in certain situations, especially when strong placebo effects are expected. The conflicting views on the ethical acceptability of sham interventions are mainly due to the exposure of a part of the research participants to risks without a chance of individual benefits. However, in **chapter 7** we argued that the risks in sham-controlled trials could be acceptable, when these are proportional to the benefits to science and society and withholding the standard of care does not lead to serious risks. While **chapter 7** shortly addressed several approaches to determine the reasonableness of risks and uncertainties in (sham-controlled) RM trials, further ethical analysis is required, as was also shown in **chapter 2**. The approaches that exist to assist researchers and Research Ethics Committees (RECs) in the risks-benefit assessment are for example the component analysis (6), the net risk test (7), and decision theory (8). However, RECs appear to make the risk-benefit judgment often on intuition instead of using systematic approaches which increases the risks of mistakes or arbitrariness (9). In **chapters 2** and **5** two aspects were described that should be included at least in systematic risk-benefit assessment: minimization of risks (e.g., by means of appropriate participant selection, intensive monitoring), and maximization of benefits (e.g., by means of valid preclinical testing, using a clinically relevant outcome measure, registration of the trial in a trial registry, publication of both positive and negative results, and allowing backwards translation).

As **chapter 7** laid the foundation for the acceptability of sham interventions, **chapter 8** provided concrete recommendations to assess the necessity and acceptability of sham

interventions or another comparator for RM trials. These recommendations were mainly directed at RM trials for disorders with a progressively declining character like degenerative orthopedic and neurodegenerative disorders. By applying the criteria of scientific necessity, reasonable risks, and adequate informed consent, as defined in **chapter 7**, it was shown that a sham procedure could often be ethically acceptable in these types of RM trials.
Chapter 8 has demonstrated that methodological principles and ethical principles in setting up clinical trials are highly interwoven, as the scientific objective influences the ethical analysis. This shows that collaboration between epidemiologists and ethicists in the field of research ethics is fruitful and should be stimulated.

Adequate participant selection in RM trials

The other main ethical challenge of setting up an RM trial is the appropriate choice of the participant group in terms of the stage of disease. In **chapters 2** and **9** four participant models were described: the *healthy volunteer* model; the *individual at risk* model; the *stable patient* model; and the *advanced stage patient* model. **Chapter 8** also distinguished the group of people in which surgery is indicated. In **chapter 2** it was shown that the inclusion of *healthy volunteers* is not ethically acceptable as a first step in RM research. In **chapter 9** it was also argued that selecting the *individual at risk* model is not ethically justifiable for first-in-human trials with RM interventions due to the high risks and uncertainties of these trials. However, this model can be ethically appropriate for testing the efficacy of RM interventions under several conditions. In contrast, *advanced stage patients* (i.e., end stage patients without any treatment options) are often most appropriate to include in a first-in-human trial with RM interventions, as these patients cannot lose much more functionality, and therefore run relatively low risks. Including *stable patients*, i.e. patients whose disease is medically controlled, in first-in-human trials could be justifiable when it concerns low risk RM interventions. Next to the extent of risks and uncertainty, also the scientific objective should determine the participant choice. What should be the scientific objective in a first-in-human RM trial was a major point of dispute in the choice for a participant group in the first embryonic stem cell trial for spinal cord injury, the Geron trial (10-12). Often first-in-human trials are primarily aimed at establishing safety and in these trials the anticipated social value should outweigh the individual risks, as no benefits to the participants are expected (13). However, the Geron trial was primarily aimed at both safety and efficacy, which was one of the reasons that early stage spinal cord injury patients were selected. Indeed, some favor that trials with such high-risk interventions should primarily aim at efficacy as high risk trials are only justifiable when potential therapeutic benefit to participants are expected (14). One of the implications of this suggestion is that participants with an open therapeutic window should be selected, i.e. patients with early stage disease. Others argued, however, that chronic, advanced stage patients would have been more appropriate in such a first-in-human trial due to the inherent high risks and uncertainties (10). Future ethics research should elaborate on the moral aspects related to this debate.

One of the challenges requiring further ethics research as well is the ethical acceptability of the *recruitment* of *individuals at risk*. Is it acceptable to ask people to screen for degenerative abnormalities in order to determine whether they are eligible for the clinical trial? In that case, these people are informed about the existence of degenerative abnormalities, while some might not want to know that they have an increased risk of developing a certain disease (15). As a consequence, it could be more justifiable to recruit only these individuals who are already aware of having these abnormalities. This ethical challenge also points at the need to reflect on the desirability of developing such preventive RM applications, on which I will elaborate in the last paragraph of this chapter.

The context in which RM research takes place

Next to these concrete ethical challenges, the context in which RM trials need to be conducted is challenging. An important aspect that affects a proper research climate is the lack of strong evidence-based medicine (EBM) practice in surgery, which was also emphasized by the orthopedic professionals in the empirical study in **chapter 3**. There is reluctance to set up surgical research and generate systematically collected evidence on the safety and effectiveness of surgical interventions, which has been called "*surgical exceptionalism*" in academic literature (16). This is partially due to the dynamics and complexity of surgical innovations, since these lead to several practical, methodological, and ethical challenges in setting up surgical clinical trials, especially randomized controlled trials (RCTs) (17-19). For example, it is difficult to standardize in surgery due the learning curve and variability in experience of surgeons as well as the difficulties of blinding surgeons and/or patients for a surgical procedure. A tailored evaluation process for surgical procedures has been suggested in literature (20;21). However, ultimately, surgical interventions should also be examined within clinical trials (preferably RCTs), as these allow reliable assessment of the long-term (side) effects (see **chapter 8**). Even though it is reasonable that RCTs are not always feasible or warranted for invasive interventions, these remain to date the default study method (17-19). It is likely that RM interventions that are minimally invasive encounter fewer hurdles than those that are more invasive. The JUVENTAS trial in **chapter 5** has demonstrated, for example, that RCTs testing invasive RM interventions are feasible and ethically acceptable. Apart from randomization and blinding, other aspects determine the rigor of a trial design; a recent review of trials testing autologous bone marrow cells in heart disease patients showed that many of these trials display discrepancies in the design, recruitment and results, such as conflicts in sample size, and statistical errors (22;23). Especially the finding that trials with fewest discrepancies tend to find less of cell interventions, stipulates that rigorous RCTs are required to acquire sound evidence (22).

Next to that, the large influence of commerce on developing and applying surgical products is also an important threat to an adequate research climate, which was also mentioned by the biomedical professionals in the empirical study as described in **chapter 3**. Indeed, commercial interests in surgery are an important driver in the introduction of innovations

to clinical practice. These interests fostered a too quick introduction to clinical practice of BMPs, lumbar disc prostheses and vertebroplasties for example, as these later all turned out to be ineffective when adequate research was conducted (24). Especially RM interventions are at risk of being pushed onto the market too early because they are often developed by small companies and sponsored by venture capitalists, who need a quick return on their investments (2).

In other words, these consequences shows that there is a need to change the culture of surgical research and practice as well as to reduce the negative influence of commercial interests, which is also likely to be beneficial for the RM field in general. Several measures could facilitate this, such as the disclosure of conflicts of interest in reported studies or improving the review of research protocols and editorial review of manuscripts (25-28).

Comparison of cardiovascular and orthopedic RM trials

Another important finding in this thesis was that similar ethical challenges appeared to arise in cardiovascular RM trials, as in orthopedic RM trials. For example, in cardiovascular patients clinical outcome measures are often affected by placebo effects as well. Thus, for testing the efficacy of RM interventions, it is scientifically necessary to blind participants and investigators by means of placebo surgery or injection. Nevertheless, **chapter 6** showed that many RCTs in the RM cardiology field do not incorporate a sham intervention, possibly because of moral concerns.
However, in certain respects, cardiovascular patients differ from the orthopedic population such as due to the increased chance of premature mortality. These patients can be considered seriously ill, relatively similar to the condition of oncology patients. It is more likely that first-in-human RM trials in cardiovascular patients are appropriate, as achieving a favorable risk-benefit ratio is more likely. Exposing relatively healthy orthopedic patients to the often high risks and uncertainties involved in a first-in-human RM trial is more difficult to justify. While advanced stage orthopedic patients could be considered seriously ill as well (due a low quality of life), potential harms could have long-term consequences since their life expectancy is not reduced due to the disease. On the other hand, injection of RM interventions in cardiovascular trials could inherently have higher risks as these are more likely to be applied systemically instead of locally. Another difference with orthopedic disorders is that cardiovascular disorders are often not limited to a specific organ, and participants often suffer from co-morbidities. The existence of vascular comorbidities can diminish cognitive capacity which can impair competence, one of the conditions for a valid informed consent procedure. Furthermore, in some degenerative orthopedic disorders diagnosis as well as prognosis is more complex than in many cardiovascular diseases. This

difficulty could complicate choosing the appropriate type of participants in orthopedic RM trials, as also discussed in **chapters 2** and **3**.

Added value of empirical studies to ethics research

Considering the limited amount of empirical literature on the ethics of translational RM, I conducted qualitative interviews with orthopedic professionals. The attitudes, opinions and experiences allowed enriching my thinking, both directly as well as subconsciously throughout this thesis. Particularly it allowed me to give insight into the world of orthopedic practice and RM research. For example, while the existence of a culture of trial and error in surgery has been described in literature, by interviewing people in the field it became clear to me that this indeed is encountered as a challenge. In other words, it brings a practice with its accompanying challenges into life. Further, it was important to note that professionals recognized similar challenges as I addressed in this thesis, which assured that my recommendations are relevant and applicable for people working in the field. Even though a topic list with themes was used to guide the interviews, I assured that there was also much space for the views of the professionals themselves. However, it is often unavoidable in qualitative research that the respondents have been influenced by the interviewer's background knowledge and ideas (29).
The results and discussion of this qualitative study are also relevant and inspiring for other RM fields. However, as only orthopedic professionals were interviewed, it would be interesting to conduct future empirical studies with professionals in other fields in which RM interventions are increasingly developed such as cardiology and neurology. Furthermore, as this was the first study on this topic, I was mainly interested in gaining a first impression of *which* societal impacts the orthopedic professionals discerned, rather than providing explanations for *why* the individual professionals recognized different impacts. This study should be regarded as a first step into planning future studies to show whether characteristics of professionals, such as age, gender, and nationality, influence their attitudes, opinions, and expectations. This requires a larger and more diverse group of respondents. In addition, this qualitative study was not aimed at generalizability but merely aimed at exploring the ethical challenges in translational RM. To assure generalizability quantitative studies, for example by means of questionnaires, could be considered for future research.

Role of ethicists in technology development

Another way in which I became acquainted with the practice of orthopedic RM was by being embedded in the IDiDAS project. We conducted ethics research parallel to this orthopedic RM research project, which allowed us to reflect on and influence the technology development

(30). Being close to a practice increases the chance to raise awareness among stakeholders of the ethical challenges involved which could also influence for example, the set-up of a planned clinical trial. Indeed, I experienced myself to be an actor within the construction of RM technology. When presenting my work at RM conferences, at consortium meetings, and in RM courses, which were often only focused on the technical, commercial, and legal aspects of developing RM interventions, I had the impression that the scientists and other stakeholders in the field welcomed the ethics perspective as a valuable additional perspective. Further, presenting our work to scientists and clinical investigators working at the departments in (orthopedic) RM appeared to make them more aware of the societal impacts of RM and the ethical aspects involved in the set-up of clinical trials.

An ethicist embedded in research projects, needs to be critical on her role and be aware of the possibility that one is relatively dependent on the funder and the research team. This was also an aspect I had to be aware of when I collaborated with investigators of the JUVENTAS trial. In this so-called *ex-post* (after completion) ethics research, we focused on evaluating the choices in the design and launch of the trial. The investigators had struggled with certain ethical challenges and were willing to share their experiences and lessons learned with the RM community. A limitation of retrospectively evaluating a trial by means of collaborating with the trial investigators is the possibility of adopting the perspective of the investigator, and possibly becoming less critical.

In short, this thesis has shown ways in which the translation of technologies can be accompanied with ethics research and as such contributes to responsible research and innovation (31).

Involving societal impacts in technology development

The working definition of responsible research and innovation (RRI) which is used in the EU program 'RRI tools' is: 'Developing better technology and innovation processes and outcomes that reflect both excellent science and the incorporation of societal values and needs (…)' (32). In other words, RRI of medical interventions like RM encompasses both anticipating and reflecting on the translational challenges of (clinical) research (T1 research), but also requires anticipation on the societal impacts of these technologies (T2 research) (33). RRI complies with the constructivist view that science and technology development is influenced by values and needs of society in which one lives. According to this view, the generation of knowledge and technologies is not only determined by empirical facts and logic, but also by societal and political factors (34;35). This means that technology developers can steer the development of the technology and can assure that the technique complies with the values and needs of society. This increases the likelihood that technologies are "successfully" received by society (31). To do so, it is essential to get a broad and rich view on the potential "hard" and "soft" societal impacts and, accordingly, its desirability and permissibility (31;36).

Hard impacts are impacts that can be expressed in numbers, such as the cost-effectiveness, the amount of eligible individuals for the novel intervention, and the calculated risks. Soft impacts concern, among others, the way in which technology alters human capacities such as behaviour, experience, and perception, which thereby can influence the vision on the definition of a good life (30). In **chapter 4** it appeared that orthopedic surgeons mentioned some soft impacts, for example, that a preventive injection could lead to giving up a healthy life style and, therefore people could feel less responsible for their health. This shows that technologies can have moral implications, as these can change the relation between humans and the environment (37). However, the professionals mainly recognized hard impacts in the domains of prevention of ageing, prevention of disease, and social justice. It is well-known that soft impacts are less frequently recognized as these are non-quantifiable, even though these are essential to take into account since these are important determinants of the wellbeing of patients (30).
In the next paragraphs I will show that these societal impacts should receive more attention, both during technology development and before the conduct of technology research in order to allow for RRI.

Anticipating and reflection during technology development

Anticipating and reflecting on the societal impacts during technology development allows steering of the technology and make a "better" technology. This also assures that the anticipated social value of clinical trials is enhanced. A part of the assessment of hard impacts can be left to experts, but particularly for assessing soft impacts it is essential to involve citizens, patient groups, and other stakeholders. This allows a broad view of perspectives on novel technologies. In turn, it allows the public to be better prepared for the technology, and in this way the public may be less surprised by the impact it may have on personal lives and on society as a whole (38). In the biomedical context, especially clinicians could be valuable in transferring these societal impacts to scientists who are actively involved in developing the technology. Depending on the type of RM intervention, several types of soft impacts can be expected. For example, some RM technologies in orthopedics could lead to treatment and even prevention of disorders related to aging such as osteoarthritis and intervertebral disc disease. Such interventions can have several impacts, and warrant reflection on the question whether preventing or treating age-related disorders corresponds with the needs and values of society. This will partially depend on whether ageing is viewed as a disease, which relates to the definition on health and disease. There is an emerging discussion on the definition of health, which can vary from complete wellbeing of the individual (39), to being able to reach one's vital goals (4), to adapt and self-manage (40). The preferred definition will also determine whether RM interventions for ageing disorders are congruent with the primary goals of health care. Broadly speaking, two opposing views exist on whether RM interventions for age-related disorders belong to the realm of health care (41). Some people view ageing as pathological and therefore as a disease. Those are likely to view health as

absence of disease and therefore are likely to welcome anti-ageing interventions (41;42). This group of people is not likely to morally object against developing RM interventions aimed at disorders related to ageing and regard these commensurable with the values of society. Others, in contrast, object to regarding ageing (disorders) as a disease and therefore are likely to discard anti-ageing RM interventions as 'enhancement'. Those are more likely to adhere to the definition of health as being able to self-adapt, which means that elderly people could change their goals and adapt to having physical problems (41). Further, those who adhere to this view are likely to regard it morally undesirable that interventions for ageing contribute to the process that more and more aspects of human life fall in the medical domain, also phrased as medicalization (43;44). Medicalization can be morally undesirable as it suggests that health is the most important value, and could lead to losing sight of other aspects that form a good life and determine successful ageing such as social functioning and satisfaction (15;38;45;46). Another consequence is that elderly are pushed into the sick role which could stigmatize elderly people as frail and incapacitated, while becoming old also has several other social meanings as elderly often take up different roles, such as being a grandparent (41).

RM interventions with preventative goals can also give rise to moral concerns related to medicalization. Additional concerns in this context are that people could be regarded responsible for their illness as interventions provide a way to avoid future disease. Further, people could lose confidence in one's body and worry about whether disease will develop (15;45;47).

Fair distribution of funding for technology research

Anticipation and reflection on the societal impacts should also receive attention in the distribution of funding for conducting medical research and technology development. As funding sources are scarce choices need to be made on how these are fairly distributed. Hard impacts like the costs per Quality Adjusted Life Year should be involved in this assessment (48). Further, also the desirability of the soft impacts of technologies needs to be involved, for which it is relevant to involve the public. Further, moral principles such as the 'fair innings' argument could be included in a fair distribution process. Fair innings means that "for healthcare resources to be distributed fairly every person should receive sufficient healthcare to provide them with the opportunity to live in good health for a normal span of years" (49). One of the implications could be that the development of RM interventions for children should have priority, especially when the view is adhered that anti-ageing interventions do not belong to the primary goals of healthcare (2;50). An example of involving society in distribution of money was demonstrated by the report of the Dutch Health Council which had several patient groups assess which innovative medical products were regarded valuable to invest in. It appeared that research into bone and cartilage regeneration, stem cell therapy for heart diseases, and skin regeneration were highly desired among all medical innovations that are being developed (51).

Future ethics research should more extensively show how the public and other stakeholders can be involved in the technology development to assure RRI. Currently, the EU program 'RRI tools' is developing a digital set of tools to advocate, disseminate, and implement RRI. One tool to enhance public deliberation about the desirability of novel RM interventions is the use of several 'techno-moral scenarios' in which potential moral consequences are imagined (52).

This thesis shows that the rise of RM brings forth many translational ethical challenges. Responsible translation to patients requires both moral reflection on the level of the design of clinical trials as well as on the societal level. Dialogue between stakeholders including technology developers, physicians, ethicists, funders, patient (organizations), and the public, should be established in an early stage of technology development to allow responsible research and innovation of RM technologies.

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Chapter 11.

Summary
Samenvatting
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Summary

Regenerative medicine (RM) technologies, such as cell-based interventions, biomaterials, and tissue engineering, are increasingly translate to patients. RM is an umbrella term for the research and clinical applications that share the scientific aspiration to restore the original function of damaged or diseased tissue by stimulating the body's own repair. In order to guarantee responsible research and innovation, it is time to systematically identify and analyze the ethical challenges involved in the translation into clinical trials and society. The field of orthopedics is used as an exemplary case in this thesis, since this field is at the front row of RM research. The scope of indications for RM in orthopedics is large and diverse, extending from interventions for degenerative disorders, such as osteoarthritis (OA) and intervertebral disc disease (IVDD), to interventions for (traumatic) defects, such as bone, meniscal and cartilage defects. While the field of orthopedics is used as an example, this thesis is relevant for other medical domains as well.

Part I Ethical and societal challenges of orthopedic Regenerative Medicine

The first three chapters of this thesis provide an overview of the ethical challenges that need to be addressed when translating orthopedic RM into clinical studies and society.

In **chapter 2** the main ethical challenges are identified that need to be addressed when considering initiating early clinical trials to test RM for orthopedic disorders. Whereas early clinical trials (also known as safety or combined safety/efficacy studies) are ethically challenging by nature, certain well-known challenges will get a new twist due to the general characteristics of RM and the application to the orthopedic population specifically. The specific characteristics of RM include novelty, complexity, new aim (compared to drugs and devices), the probable effectiveness in early stage, and invasiveness, while the orthopedic patient group is characterised by their relatively healthy status (in the sense of having a non-lethal disorder), the availability of (end-stage) treatments, and the difficulty of diagnosis and prognosis. The identified challenges are: assessment of risks and benefits; designing a study in terms of outcome measures and comparators; and participant selection. These challenges are particularly intensified in RM research that aims to apply these approaches in *degenerative* musculoskeletal disorders, such as OA and IVDD.

Reaching proportionality between the (uncertainties of) risks and the expected benefits is a salient issue. Due to the novelty and complexity of RM interventions the uncertainty of risks is relatively high, and due to its invasiveness some physical risks are implicated per se. Applying these interventions in an orthopedic patient which is often relatively healthy (no heightened mortality rate) is particularly challenging. The choice for outcome measures in a clinical trial is difficult in orthopedic RM as no hard endpoint is available that assesses functional or structural condition and correlates with clinical symptoms. Further, the time till the endpoint is preferably long to gain knowledge on the working mechanism of RM interventions, but this increases risks and burden to participants.

Another main challenge is the choice of the most appropriate comparator. There is a strong consensus that participants should not be withheld an intervention that provides a net medical advantage, which implies that any experimental RM intervention should first be compared against the standard of care, if available. However, especially for degenerative orthopedic disorders, such as OA and IVDD, no therapies are currently available that prevent or reverse the progress of degeneration. For those musculoskeletal disorders a placebo as a comparator could be preferable. Since RM products will usually have to be implanted via minimally invasive surgery or injection, a placebo surgery/injection, also known as a sham intervention, is required. However, a sham intervention is ethically contentious due to the inherent risks without any potential benefits for the participant.
The last main ethical challenge is the choice of the appropriate participant group to enroll in RM trials. Advanced-stage orthopedic patients are in a late stage of progression: the original tissue, such as articular or intervertebral disc cartilage, is hardly present any more and has been replaced by scar/fibrous tissue. To assess the safety (and potential efficacy) of RM interventions, advanced stage patients might be most appropriate to include as a first step, as these patients cannot lose much functionality anymore. Stable disease patients in orthopedics are patients with an early stage of degeneration that has led to symptoms and minor 'objective' abnormalities. It seems most ethically justified to include stable patients in a study on RM interventions when safety has already been established.

Chapters 3 and **4** describe the results of the empirical research in which 36 biomedical professionals working at the front lines of orthopedics and/or RM were interviewed. The respondents were mainly orthopedic surgeons, biologists and biomedical engineers.
Chapter 3 identifies the attitudes, opinions, and experiences of the professionals regarding the ethical issues in the translation of RM to (early) clinical trials. Although professionals welcomed the increasing (preclinical) research into RM interventions for orthopedic disorders, they addressed four challenges in the translation to clinical research, especially for degenerative musculoskeletal disorders. The first two were the acceptability of risks and participant selection which were identified in **chapter 2** as well. The third challenge consisted of the need to discuss the aim of RM research, varying from regenerating tissue to improving well-being of patients. Some respondents favored clinical studies that aim at outcome measures capturing well-being so as to inform clinical practice, whereas others favored gaining scientific knowledge about the mechanism of action of RM. The fourth main challenge was how to obtain valid and reliable research results in the current context in which orthopedic surgery lacks a strong tradition of evidence-based medicine practice. Surgeons were furthermore worried that the role of commerce in RM, similar to surgical research and clinical practice, could cause conflicts of interest that negatively affect the integrity of researchers and the scientific validity of clinical studies. An important conclusion from this qualitative study was that RM could form an impetus to address and improve evidence based practice in orthopedics, and to stimulate responsible innovation and collaboration

among industry, researchers, surgeons, and other partners. As a consequence, not only the orthopedic RM field alone will benefit from proper efforts to promote ethically and scientifically sound translation into clinical research, but also the orthopedic field as a whole.

In **chapter 4** the attitudes, opinions and expectations of orthopedic biomedical professionals regarding the societal impacts of RM are identified. When considering this step to society the *hard impacts* can be taken into account, such as the potential risks of a technology, cost-effectiveness of an intervention, and the economic value. However, a new technology can also have *soft impacts*, in the sense that it influences our moral actions, experiences, perceptions, and interactions with others, and as such have an impact on our quality of life. Three main domains of societal impacts were mentioned by the professionals: prevention of ageing, prevention of disease, and social justice. Mainly the hard sides of impacts were discerned rather than the soft impacts. Professionals appeared not to regard themselves as actors in the societal debate, as hardly any remarks are made on how they can become co-responsible for these societal impacts.
The main domains that were mentioned by the professionals also return in debates on other emerging medical technologies, but RM brings in new considerations. Novel is that RM technologies could probably intervene in a quite early stage in ageing and thereby could postpone ageing up to a certain extent. Furthermore, what makes RM interventions particularly challenging is the extensive degree of prevention they could encounter and the invasive manner of prevention. Further, RM could have a large influence on the gap in health status between rich and poor (social injustice), as only a small part of society being able to afford RM technologies.
Based on the results, it is recommended that professionals take up their role as actor and become more involved in the societal debate. This is important as they can co-shape the societal impacts during the developmental process of technologies. Via this way, RM interventions are more likely to be successfully received by society.

Part II Ethical challenges of cardiovascular Regenerative Medicine

The next two chapters describe the ethical challenges that arise when translating cardiovascular RM interventions into clinical trials.
In **chapter 5** the JUVENTAS trial serves as an example to identify the ethical challenges in the design and launch of stem cell randomized controlled trials (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. The choices and considerations of the JUVENTAS team regarding the key ethical challenges in this trial are retrospectively evaluated: assessment of risks and benefits, the choice for outcome measures, the choice for the comparator, the appropriate selection of participants, and adequate informed consent. This results in considerations for the design of future stem cell RCTs: first, one should be aware that assessing risks and benefits is more challenging as the novel character

and complex nature of stem cells cause more uncertainty in comparison to traditional pharmaceuticals. In addition, the invasiveness of the intervention, randomization, and the inclusion of a sham intervention cause physical risks and psychological burden. One should make sure to manage and, if possible, minimize risks. Furthermore, benefits of the study should be enhanced by gaining knowledge that stimulates backward translation and information about working mechanism, instead of only knowledge to move to a next trial. Second, however, the primary outcome measures of these RCTs should reflect clinical improvement as this is considered to be more relevant for future patients. Third, due to the invasiveness of stem cell-based interventions and increased likelihood of placebo effects due to the hype of the field, sham interventions are considered methodologically necessary. However, sham interventions are only ethically acceptable when physical and psychological risks are proportionate to the scientific and societal benefits, and when other conditions such as gaining valid informed consent are fulfilled. Fourth, one should consider which participant group is most appropriate. This depends, among others, on the aim of the study, and the toxicity of the intervention. 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, when advanced stage patients are included one should be aware that obtaining informed consent is more challenging as they are more likely to misunderstand the purpose, risks, and potential benefits of the trial. The risk of misunderstanding 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.

In **chapter 6** one of the key ethical challenges identified in **chapter 5** is further explored: the choice for a sham intervention as a comparator. By means of a literature search it was shown to what extent sham interventions have been used in clinical trials testing autologous cell-based interventions in patients with ischemic heart disease (IHD). A total of 56 RCTs were identified that were published between 2001 and 2013. A major conclusion from this study was that 39% of RCTs investigating efficacy of autologous cell intervention used a double-blind trial design based on a sham procedure. This shows that the choice for the control group for cell-based interventions in cardiology highly differs, which could be related to diverging views on scientific necessity and ethical acceptability of sham. The diversity in the choice of the comparator supports the need to clarify when and under what conditions sham is scientifically necessary and ethically acceptable, and when another comparator is more appropriate in clinical trials investigating cell-based interventions. **Chapter 7** provides an overview of the general considerations regarding ethical acceptability of sham interventions, while **chapter 8** particularly addresses the appropriate comparator selection in RM trials, including cell-based interventions.

Part III: Normative guidance on key ethical challenges in Regenerative Medicine

Chapter 7 ethically evaluates the arguments in favor and against using sham interventions in clinical trials, as presented in literature. Arguments in favor of sham interventions are that these increases the scientific validity and the benefits to society, while at the same time the risks and harm can be acceptable. Arguments against sham interventions include that these pose unacceptable risks to participants, encounter difficulties with informed consent, the use of deceptive tactics is unethical, and the feasibility is compromised due to a lack of public support. None of the papers fully reject sham interventions and many regard sham acceptable provided the conditions of scientific necessity, reasonable risks, and valid informed consent are fulfilled. Therefore, it is concluded that further debate should no longer address *whether* sham is ethically acceptable, but rather *when* these conditions are fulfilled.

Chapter 8 provides the main ethical considerations in the comparator selection in RM trials. The choice of the comparator is largely determined by the objective of the intervention. Some RM interventions aim to prevent disease and are therefore applied in an at risk stage of disease. Others are aimed at patients with early stage disease and have the objective to return to a healthy state or at least to slow progression. RM interventions applied at the moment that surgery is indicated can be aimed at substituting the surgical treatment or at supplementing surgical treatment. RM interventions applied pre-operatively are aimed at postponing surgery, while RM applied post-operatively are aimed at improving the outcome of surgery. RM in a late stage of disease is aimed at slowing progression of disease. By applying the criteria of scientific necessity, reasonable risks, and adequate informed consent, as defined in **chapter 7**, it is shown that a sham procedure can often be ethically acceptable in trials testing RM interventions. However, in RM trials aimed at preventing disease the risks to the sham group are high and are not likely to outweigh the uncertain benefits to society. In addition, gaining adequate informed consent is likely to be compromised. In RM trials focused on substituting surgical treatment the use of the existing surgery as a control is ethically preferable, since this allows showing relative efficacy and prevents withholding an established effective intervention to the control group.

In **chapter 9** the appropriate choice of participants in RM clinical trials is ethically evaluated. As **chapter 8** shows that one of the aims of RM interventions is to prevent disease, it is expected that future RM clinical trials will consider testing these in individuals the intervention is aimed at: individuals at risk of clinical disease. However, so far the debate on participant selection (based on stage of disease) in the research ethics literature centres around three other participant models: the *healthy volunteer* model; the *stable patient* model; and the *advanced stage patient* model. This chapter therefore mainly evaluated the ethical challenges of this fourth participant model: *the individual at risk* model. Three main challenges of selecting the individual at risk model for testing RM interventions were discussed: achieving risk-benefit proportionality; designing an efficacy trial in terms of follow-up and sample size; and

obtaining valid informed consent. Generally speaking, selecting this 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 individuals should be at high risk of developing disease; robust preclinical evidence of efficacy needs to be present; and the informed consent procedure should contain extra safeguards.

In **chapter 10** the main findings of this thesis are discussed and questions for further research were provided. Further, the contribution of empirical studies to ethical analysis and the role of ethics research in technology development is evaluated. Last, RM technology is put in a broader societal perspective. One of the main findings of this thesis is that conducting early orthopedic RM clinical trials is challenging, both due the climate in which RM trials need to be conducted as well as due to concrete ethical challenges. These ethical challenges are no different from "traditional" drug trials, although RM technologies place those challenges in a new context. Furthermore, similar ethical challenges appeared to arise in cardiovascular RM trials, as in orthopedic RM trials. Nevertheless, these patient populations and the accompanying RM interventions also differ and therefore give a specific twist to some of these challenges.

A question for future research is what first-in-man trials with high risk interventions like RM should primarily strive for: safety or efficacy. This will also require considerations related to participant selection as the scientific objective is one of its determinants. Another question of future ethics research concerning participant selection is the ethical acceptability of the recruitment of individuals at risk.

This thesis shows how the translation of RM technologies can be accompanied with ethics research, as this project was embedded in a consortium developing a RM technology. Parallel ethics research allows ethicists to influence the technology development and thereby stimulate responsible translation of RM technologies. This complies with the constructivist view on science and society that technology development is also influenced by other factors than scientific aspects. Responsible research requires both anticipation and reflection on the ethical challenges in the design of clinical trials and the hard and soft societal impacts of the technology. Assessment of hard impacts can largely be left to experts, but particularly for assessing soft impacts it is essential to involve the public and other stakeholders. In turn, it allows the public to be better prepared for the technology, and in this way the public will be less surprised by the impact it may have on personal lives and on society as a whole. Future ethics research should more extensively how the public and other stakeholders can be involved in RM development to assure responsible research and innovation.

Samenvatting

Het veld van de regeneratieve geneeskunde (RG) is sterk in ontwikkeling. RG is een verzamelbegrip voor het onderzoek naar het herstel van beschadigd weefsel, oftewel regeneratie, en de klinische toepassingen ervan. Toepassingen zijn bijvoorbeeld het gebruik van (stam)cellen, biomaterialen en het transplanteren van gekweekt weefsel. Hoewel veel van deze technieken nog worden getest in lab- en dierexperimenten, worden deze technieken in toenemende mate ook vertaald naar onderzoek met mensen en soms ook al toegepast bij patiënten. Om op een verantwoorde wijze deze omzettingen te maken is het belangrijk de ethische uitdagingen te herkennen en analyseren. In dit proefschrift is met name de orthopedie, het vakgebied van de bot-, spier- en gewrichtsaandoeningen, als voorbeeld gebruikt voor deze ethische analyse, aangezien dit een van de voorlopers is in het onderzoek binnen de RG. Er is een grote variatie aan orthopedische indicaties waarvoor RG-technieken worden ontwikkeld, zoals artrose van de knie en tussenwervelschijfdegeneratie (leidend tot knie-of rugpijn en/of bewegingsbeperking), tot aan interventies voor traumatische aandoeningen, bijvoorbeeld botbreuken of kraakbeendefecten. Ondanks dat de orthopedie, maar ook de cardiologie, in dit proefschrift regelmatig wordt aangehaald is dit proefschrift ook van toepassing op andere medische vakgebieden.

Deel 1: Ethische en maatschappelijke uitdagingen van regeneratieve geneeskunde binnen de orthopedie

De eerste drie hoofdstukken van deel 1 geven een overzicht van de belangrijkste ethische kwesties bij het vertalen van RG-technieken binnen de *orthopedie* naar het wetenschappelijk onderzoek met mensen en de maatschappij.

In **hoofdstuk 2** worden de belangrijkste ethische vraagstukken bij het opzetten van onderzoek met mensen besproken. Het opzetten van onderzoek naar interventies die voor het eerst in mensen worden getest (fase I of fase I/II studies) is altijd ethisch uitdagend. Maar door de kenmerken van RG- technieken en de toepassing bij orthopedische aandoeningen in het bijzonder, krijgen de vraagstukken een nieuwe draai. RG-technieken zijn nieuw, complex, hebben een nieuw doel van regeneratie (ten opzichte van medicijnen en hulpmiddelen zoals protheses) en zijn invasief (m.a.w. behoeven vaak een injectie of chirurgische ingreep). Patiënten met een orthopedische aandoening zijn relatief gezond, aangezien ze vaak niet levensbedreigend ziek zijn. Daarnaast hebben ze vaak nog behandelmogelijkheden zoals een prothese en kan het diagnosticeren van een orthopedische aandoening lastig zijn, vooral bij degeneratieve aandoeningen zoals artrose. Deze combinatie van kenmerken zet de volgende ethische kwesties in een nieuw licht: de risico-baten evaluatie, de keuze voor uitkomstmaten en controles en de selectie van het type deelnemers.

Het verkrijgen van een aanvaardbare verhouding tussen risico's en verwachte baten van RG-technieken wordt bemoeilijkt doordat deze inherent risicovol zijn. Dit komt doordat deze invasief zijn en de risico's lastig te voorspellen zijn door de complexiteit van de technieken.

Omdat deze (potentieel) risicovolle technieken in een relatief gezonde populatie worden toegepast is dit extra uitdagend aangezien deze personen veel te verliezen hebben.
De keuze voor de uitkomstmaten is problematisch doordat er geen harde maten beschikbaar zijn die goed correleren met verbetering van de symptomen van de deelnemers. Daarnaast is het wenselijk om de deelnemers langdurig te volgen om informatie te verkrijgen over het werkingsmechanisme van dit soort interventies, maar dit verhoogt de belasting voor deelnemers.
Een ander belangrijk vraagstuk is wat de meest geschikte controle is wanneer een gerandomiseerde studie wordt opgezet. Gerandomiseerde studies hebben tot doel de werkzaamheid van een interventie te onderzoeken: een deel van de deelnemers ontvangt de interventie en het andere deel, de controlegroep, krijgt deze niet maar soms wel een bestaande behandeling of een placebo. Indien een behandeling bestaat die redelijke medische baten oplevert, een zogenaamde 'standard of care', mag deze niet worden onthouden aan de deelnemers. Dit betekent dat elke RG-interventie in principe vergeleken moet worden met deze standard of care. Er zijn echter vooral voor degeneratieve orthopedische aandoeningen momenteel geen behandelingen die regeneratie voorkomen of bevorderen. In die gevallen kan het aanvaardbaar en wenselijk zijn een placebo als controle te gebruiken om wetenschappelijk valide resultaten te verkrijgen. Aangezien RG-interventies meestal met behulp van minimaal invasieve chirurgie of injecties moeten worden toegediend, is placebochirurgie of injectie nodig, ook wel invasieve placebo genoemd. Placebochirurgie heeft echter inherente risico's zonder kans op baten voor de patiënt, wat morele bezwaren met zich meebrengt.
Als laatste is het belangrijk stil te staan bij de vraag welke groep van deelnemers, gebaseerd op ziektestadium, het meest geschikt is om te includeren. Er bestaan drie modellen die het type deelnemers beschrijven: gezonde vrijwilligers, stabiele patiënten en patiënten in een vergevorderd stadium van ziekte. Patiënten in een vergevorderd stadium van hun ziekte zijn het meest aanvaardbaar om in vroegefasestudies te includeren voor het testen van orthopedische RG-technieken. Stabiele patiënten zijn in een vroeg stadium van regeneratie en hebben matige symptomen. Het is aanvaardbaar om stabiele patiënten te includeren in latefasestudies wanneer veiligheid al is aangetoond.

Hoofdstukken 3 en **4** beschrijven de resultaten van de 36 kwalitatieve interviews die ik heb gehouden met professionals op het gebied van de orthopedie en/of de regeneratieve geneeskunde. De respondenten waren vooral orthopedische chirurgen en basaal onderzoekers.
Hoofdstuk 3 beschrijft de houding, meningen en ervaringen van deze professionals rondom de ethische kwesties bij de vertaling van RG-technieken naar klinische studies. Ondanks dat zij het (pre)klinisch onderzoek naar deze interventies verwelkomden, gaven ze ook vier ethische uitdagingen aan. Twee van deze kwesties draaiden om de aanvaardbaarheid van de risico's en de keuze voor het type deelnemers, zoals ook wordt besproken in **hoofdstuk 2**.

Daarnaast gaven zij aan dat er debat nodig is over het doel van RG-onderzoek: moet dit primair gericht zijn op de regeneratie van weefsel of op het verbeteren van het welzijn van patiënten? Sommigen gaven de voorkeur aan uitkomstmaten die het welzijn van patiënten reflecteren, terwijl anderen een voorkeur hadden voor het vergaren van wetenschappelijke kennis over het werkingsmechanisme van RG.
Verder gaven de respondenten aan dat het belangrijk is dat aandacht wordt besteed aan de mogelijkheid om valide en betrouwbare onderzoeksresultaten te verkrijgen in de context van de orthopedische chirurgie waarin een traditie van 'evidence-based medicine' ontbreekt. Daarnaast constateerden de chirurgen dat de invloed van commercie binnen de RG belangenconflicten met zich mee kan brengen waardoor de integriteit van onderzoekers en de validiteit van klinische studies op het spel staan.
Uit de resultaten van dit kwalitatieve onderzoek wordt afgeleid dat de RG een stimulans kan geven aan het verder ontwikkelen van de orthopedie als een evidence-based praktijk en aan een verantwoorde manier van samenwerking tussen industrie, onderzoekers en chirurgen. Hierdoor zal niet alleen de RG profiteren van het opzetten van moreel en wetenschappelijk verantwoord onderzoek, maar ook de orthopedie als geheel.

In **hoofdstuk 4** worden de houdingen, meningen en verwachtingen van de professionals rondom de maatschappelijke impacts van RG beschreven. Wanneer de vertaalslag van een nieuwe technologie naar de maatschappij wordt gemaakt, moeten zowel 'harde' impacts als 'zachte' impacts mee worden genomen. De harde impacts zijn bijvoorbeeld de risico's, de kosteneffectiviteit en de economische waarde van de nieuwe technologie. De zachte impacts zijn de gevolgen die de technologie kan hebben op onze morele gedragingen, ervaringen, percepties en interactie met anderen.
De drie domeinen van maatschappelijke impacts waarop de professionals verwachtten dat RG impact zou kunnen hebben, waren de preventie van ouderdom, de preventie van ziektes en maatschappelijke rechtvaardigheid. De harde impacts in deze domeinen werden voornamelijk herkend, terwijl de zachte impacts nauwelijks herkend werden. Daarnaast bleken de professionals zich niet als actoren in het maatschappelijke debat te gedragen aangezien ze zich niet (mede)verantwoordelijk opstelden ten aanzien van deze impacts.
De domeinen die de professionals noemden zijn ook te herkennen in andere debatten rondom nieuwe technologieën, maar RG voegt daar aspecten aan toe. Nieuw is namelijk dat RG in een zeer vroeg stadium van ouderdom zou kunnen ingrijpen en daarmee (de ongemakken van) ouderdom zou kunnen voorkomen. Daarnaast is de mate van preventie die RG kan bereiken groot, wat bovendien via een invasieve wijze zal gebeuren. Tevens kan RG een grote invloed hebben op het verschil in gezondheid tussen rijk en arm aangezien deze dure technologieën waarschijnlijk slechts door een deel van de bevolking kan worden bekostigd.
Wij concludeerden op basis van deze studie dat professionals meer betrokken moeten zijn in het maatschappelijke debat rondom RG, naast andere betrokkenen. Zij zijn namelijk

degenen die de maatschappelijke impacts ook kunnen beïnvloeden aangezien zij de techniek (mede)ontwikkelen. Hierdoor is de kans groter dat technologieën worden ontwikkeld met aanvaardbare maatschappelijke impacts.

Deel II: de ethische uitdagingen van regeneratieve geneeskunde binnen de cardiologie

De volgende twee hoofdstukken beschrijven de ethische kwesties bij de omzetting van RG-technieken binnen de *cardiologie* naar klinische studies.
In **hoofdstuk 5** dient de JUVENTAS studie als een voorbeeld om de ethische kwesties in kaart te brengen van het opzetten van gerandomiseerde gecontroleerde studies naar stamcellen. De JUVENTAS studie onderzocht de werkzaamheid van autologe beenmergcellen bij patiënten met ernstig perifeer vaatlijden door middel van een dubbelblind placebo-gecontroleerde studie. Retrospectief worden de keuzes en overwegingen van het JUVENTAS team rondom de ethische dilemma's geëvalueerd. Dit resulteert in overwegingen en aanbevelingen voor toekomstige gerandomiseerde studies naar stamcellen. Ten eerste is het belangrijk ervan bewust te zijn dat het beoordelen en evalueren van de risico's en baten moeilijk is doordat door het nieuwe en complexe karakter van stamcellen veel onzekerheid over de risico's en baten bestaat. Daarnaast leiden de invasieve procedure, de randomisatie en het gebruik van placebochirurgie zowel tot fysieke risico's als psychologische belasting. De risico's moeten zoveel mogelijk geminimaliseerd worden en de mogelijke baten moeten verhoogd worden door o.a. kennis te vergaren over het werkingsmechanisme van stamcellen. Ten tweede, is het aanbevolen in gerandomiseerde studies uitkomstmaten te gebruiken die relevant zijn voor patiënt, zoals kwaliteit van leven. Ten derde is het gebruik van een invasieve placebo als controle wenselijk door de verhoogde kans op placebo-effecten door de hype van het stamcelveld. Een invasieve placebo is echter alleen moreel aanvaardbaar wanneer de fysieke en psychologische risico's proportioneel zijn aan de wetenschappelijke en maatschappelijke baten van de studie en wanneer aan de voorwaarden van informed consent is voldaan. Ten vierde is het belangrijk te bedenken welke groep deelnemers het meest geschikt is te includeren, wat onder andere afhangt van het doel van de studie en de toxiciteit van de interventie. Eventuele risico's hebben het minste impact bij cardiovasculaire patiënten in een vergevorderd, ernstig stadium van hun ziekte, maar de kans op baten is ook laag in deze groep. Ten vijfde, wanneer patiënten in een vergevorderd stadium worden geïncludeerd moet er rekening mee worden gehouden dat het verkrijgen van informed consent bemoeilijkt wordt doordat de kans groot is dat het doel, de risico's en de mogelijke baten niet goed worden begrepen. Het risico op misverstanden is vergroot doordat de interventie invasief is en door de grote belofte van RG. Er bestaat een morele plicht om te zorgen dat de informatie adequaat is en de deelnemers deze informatie goed hebben begrepen.

In **hoofdstuk 6** wordt een van de ethische kwesties onderzocht die in **hoofdstuk 5** werd geïdentificeerd: de keuze voor een invasieve placebo als een controle. Door middel van een

literatuuronderzoek werd uitgezocht in welke mate klinische studies met autologe cellen voor patiënten met ischemische hartaandoeningen een invasieve placebo hebben gebruikt. In totaal voldeden 56 gerandomiseerde studies tussen 2001 en 2013 aan de inclusiecriteria. Een van de belangrijkste conclusies was dat 39% van de studies de effectiviteit van de cellen onderzochten door middel van een dubbelblinde studie met gebruikmaking van een invasieve placebo. Dit laat zien dat de keuze voor de controle bij het testen van cellen binnen onderzoeksteams verschilt, wat verband kan houden met verschil in visie op de wetenschappelijke noodzaak en morele aanvaardbaarheid van placebochirurgie.
Deze bevindingen illustreren het belang om te verhelderen wanneer en onder welke voorwaarden een invasieve placebo wetenschappelijk noodzakelijk en moreel aanvaardbaar is, dan wel wanneer een andere controle meer geschikt is. **Hoofdstuk 7** omvat de algemene overwegingen rondom de morele aanvaardbaarheid van placebochirurgie, terwijl **hoofdstuk 8** specifiek de juiste keuze van de controle in RG-trials bespreekt.

Deel III: Aanbevelingen voor de ethische uitdagingen van de Regeneratieve Geneeskunde

Hoofdstuk 7 evalueert de argumenten in de literatuur voor en tegen het gebruik van invasieve placebo in klinische studies. De argumenten voor het gebruik van placebochirurgie zijn dat het de wetenschappelijke validiteit en de baten voor de maatschappij verhoogt en dat de risico's en schade aanvaardbaar kunnen zijn. Argumenten tegen het gebruik van placebochirurgie zijn dat deze onaanvaardbare risico's voor de deelnemers kunnen geven, de informed consent-procedure bemoeilijken, het gebruik van misleidende tactieken immoreel is en dat de haalbaarheid van dit soort studies beperkt wordt door maatschappelijke weerstand. Geen van de artikelen bleek het gebruik van placebochirurgie volledig onaanvaardbaar te vinden en alle beschouwden het gebruik aanvaardbaar wanneer aan de voorwaarden van wetenschappelijke noodzaak, redelijke risico's en informed consent was voldaan. We concluderen dat het ethische debat zich niet langer moet richten op de vraag *of* placebochirurgie aanvaardbaar is, maar op de vraag *wanneer* aan de voorwaarden is voldaan.

Hoofdstuk 8 bevat de belangrijkste ethische overwegingen in de keuze van de controle in RG- studies. De keuze wordt voornamelijk bepaald door het doel van de RG-interventie. Sommige RG-interventies hebben ten doel het voorkomen van ziekte. Deze interventies worden toegepast wanneer er nog geen symptomen zijn. Anderen worden bedoeld voor patiënten met milde symptomen waarbij vooral het doel is gezond te worden of ten minste de ziekte te vertragen. Een RG-interventie kan ook ten doel hebben een bestaande operatie te vervangen of de operatie te verbeteren door de RG-interventie toe te voegen aan de operatie. Andere RG-interventies worden preoperatief toegepast met als doel de operatie uit te stellen of postoperatief om de uitkomst van de operatie te verbeteren. RG in een laat stadium van de ziekte is vaak gericht op het vertragen van de ziekte. Aan de hand

van de criteria van wetenschappelijke noodzaak, redelijke risico's en informed consent die werden geformuleerd in **hoofdstuk 7**, wordt beschreven dat placebochirurgie vaak ethisch aanvaardbaar is in RG-studies. In RG-studies gericht op het voorkomen van ziekte zijn de risico's voor de controlegroep echter groot en deze wegen niet op tegen de mogelijke baten voor de samenleving. Ook wordt het verkrijgen van informed consent bemoeilijkt. Bij het testen van een RG-interventie gericht op het vervangen van een chirurgische ingreep wordt bij voorkeur de huidige chirurgische ingreep als controle gebruikt, omdat een dergelijk studie aan kan tonen of de interventie relatief gezien effectief is. Dit voorkomt dat een effectieve interventie wordt onthouden aan de controlegroep.

In **hoofdstuk 9** vindt een ethische analyse plaats van de keuze voor het type deelnemers in RG studies. Aangezien **hoofdstuk 8** laat zien dat sommige RG-interventies gericht zijn op de preventie van aandoeningen, wordt verwacht dat RG-studies zullen worden opgezet met mensen die nog niet ziek zijn maar risico hebben op de ziekte. Er is echter nog nauwelijks debat geweest over de ethiek van het includeren van dergelijke deelnemers. Tot nog toe heeft het debat rondom de keuze van de deelnemers zich gericht op drie andere modellen van deelnemers: *gezonde vrijwilligers*, het *stabiele patiënt* model en het *laatstadium patiënt* model. In **hoofdstuk 9** worden de drie belangrijke uitdagingen van het selecteren van mensen met risico op ziekte besproken: het verkrijgen van een proportionele balans tussen risico's en baten, de complexiteit van het opzetten van een studie en het verkrijgen van informed consent. Over het algemeen is het selecteren van deze mensen niet aanvaardbaar voor vroegefasestudies naar RG-interventies met hoge risico's en onzekerheden. Het kan echter moreel aanvaardbaar zijn in late-fasestudies wanneer aan de volgende voorwaarden is voldaan: de te testen interventie heeft een laag risico, de deelnemers hebben een grote kans op het ontwikkelen van ziekte, er bestaat sterk preklinisch bewijs dat de te testen interventie effectief is en de informed consent-procedure bevat voorzorgsmaatregelen met betrekking tot de communicatie van onzekerheden.

In **hoofdstuk 10** worden zowel de belangrijkste bevindingen van dit proefschrift beschreven als vragen voor toekomstig onderzoek opgeworpen. Tevens wordt teruggekeken op de bijdrage van het kwalitatieve onderzoek aan de ethische analyse en wordt de rol van ethiekonderzoek binnen technologieontwikkeling onderzocht. Daarnaast wordt de ontwikkeling van de regeneratieve geneeskunde in maatschappelijk perspectief geplaatst. Een van de belangrijkste bevindingen van dit proefschrift is dat het opzetten van klinische studies naar RG interventies binnen de orthopedie en andere vakgebieden uitdagend is. Dit komt zowel door het klimaat waarbinnen RG-studies moeten worden uitgevoerd als door concrete ethische uitdagingen. Deze laatste zijn niet anders dan in medicijnstudies bijvoorbeeld, maar plaatsen RG-technieken in een nieuwe context. Daarnaast blijken dezelfde soort ethische vraagstukken ook in cardiovasculaire RG-studies plaats te vinden. Desondanks verschillen zowel de studiepopulaties als de RG-interventies in enkele opzichten van elkaar

waardoor de ethische kwesties in een nieuw licht komen te staan. Een belangrijke vraag die in vervolgonderzoek aan de orde moet komen is welk doel vroegefasestudies naar hoog-risico RG-interventies na moeten nastreven: veiligheid of effectiviteit. Dit is vooral relevant voor de ethische kwestie van de keuze van de deelnemers omdat deze wordt beïnvloed door het wetenschappelijke doel. Een andere vraag voor vervolgonderzoek rondom de keuze voor de deelnemers is of en wanneer het moreel aanvaardbaar is dat mensen die nog niet ziek zijn maar risico lopen op ziekte worden gerekruteerd voor deelname aan wetenschappelijk onderzoek. Daarnaast toont dit proefschrift aan hoe technologieontwikkeling kan worden begeleid met ethiek onderzoek aangezien dit project deel uitmaakte van een consortium dat een RG-interventie ontwikkelde. Ethiekonderzoek parallel aan techniekontwikkeling maakt het mogelijk dat ethici de techniek kunnen beïnvloeden en daarmee bijdragen aan een (maatschappelijk) verantwoorde technologieontwikkeling. Dit past bij de constructivistische visie op wetenschap en samenleving waarin techniekontwikkeling ook wordt beïnvloed door andere factoren dan wetenschappelijke aspecten. Verantwoord innoveren in de geneeskunde behoeft anticipatie en reflectie op zowel de ethische uitdagingen bij het opzetten van klinische studies als op de harde en zachte impacts van de technologie op de maatschappij. Beoordelen van de harde impacts kan deels worden overgelaten aan professionals, maar voor de evaluatie van zachte impacts is het essentieel om publiek en gebruikers te betrekken. Dit zorgt er ook voor dat de maatschappij beter voorbereid is op zulke technologieën. Toekomstig ethiekonderzoek moet zich richten op de manieren waarop de maatschappij en andere actoren op een juiste manier bij de ontwikkeling van RG-interventies kunnen worden betrokken.

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Curriculum Vitae

Sophie Niemansburg was born on the 15th of November 1985 in Rotterdam, The Netherlands. In 2003 she obtained her diploma at the Erasmiaans Gymnasium in Rotterdam. In the same year she started her medical training at the University Medical Center Utrecht (UMCU). In 2004 she received her propaedeutic exam cum laude. Gradually she developed an interest in medical ethics. To increase her knowledge on ethics, she took courses in Philosophy, such as 'philosophical ethics', 'normative ethics' and 'philosophy of science' at the University of Utrecht. Furthermore, she did a research internship at the department of Medical Ethics of the Julius Center (UMCU) under supervision of prof. dr. J.J.M. van Delden. Also her enthusiasm for the field of public health after two internships at the GGD (Gemeentelijke Gezondheidsdienst) grew. She was also impressed in a different manner by her internship at the trauma surgery department of a hospital in Stellenbosch, South Africa.

After receiving her medical degree in 2010, she worked as a resident at the Neurology department of the Diakonessenhuis in Utrecht. Due to her high interest in medical ethics she applied for a 3-year PhD project at the department of Medical Humanities (the name was changed in the meantime), supervised by dr. A.L. Bredenoord, prof. dr. W.J.A. Dhert and prof. dr. J.J.M. van Delden. In October 2011 she started with her thesis 'The Ethics of Bringing Regenerative Medicine to Patients: the example of orthopedics'. The thesis formed part of Project P2.01 IDiDAS of the research program of the BioMedical Materials Institute. During her thesis she also taught medical ethics at undergraduate, graduate level and postgraduate level at the UMC Utrecht.

After finishing her manuscript, it became time to specialize in her other interest: the public health. In February 2015 she started her training as a consultant Infectious Disease Control at the GGD Flevoland.

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